

Effect of risk propensity on treatment understanding and decisions in MS patients

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Acronyms

ANOVA	Analysis of Variance
BDI-II	Beck Depression Inventory-II
BICAMS	Brief International Cognitive Assessment for MS
BRIMMS	Benefit and Risk Information for Medication in Multiple Sclerosis
BVMT-R	Brief Visuospatial Memory Test- Revised
CIS	Clinically Isolated Syndrome
CVLT-II	California Verbal Learning Task II
DCS	Decisional Conflict Scale
DMD	Disease-modifying Drug
EDSS	Expanded Disability Status Scale
EPHPP	Effective Public Health Practice Project
FSS	Fatigue Severity Scale
HADS	Hospital Anxiety and Depression Scale
HBM	Health Behaviour Model
IES	Impact of Events Scale
IGT	Iowa Gambling Task
JCV	John Cunningham virus
MS	Multiple Sclerosis
PDDS	Patient Determined Disease Steps
PML	Progressive Multifocal Leukoencephalopathy
PPMS	Primary Progressive Multiple Sclerosis

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRMS	Progressive Relapsing Multiple Sclerosis
RAS	Risk Acceptance Score
RPS	Risk Propensity Scale
RRMS	Relapsing Remitting Multiple Sclerosis
SDMT	Symbol Digit Modalities Test
SPMS	Secondary Progressive Multiple Sclerosis
TRAL	Therapy-related Acute Leukaemia
VAS	Visual Analogue Scale
WTAR	Wechsler Test of Adult Reading

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1. Executive Summary

1.1. General background

Multiple Sclerosis (MS), a leading cause of neurodisability, is a chronic inflammatory disorder of the central nervous system (Thompson, Baranzini, Geurts, Hemmer, & Ciccarelli, 2018). The condition causes changes including sensation, mobility, balance, sphincter, vision and cognition symptoms (Brownlee, Hardy, Fazekas, & Miller, 2017). Although there is no cure for MS, disease-modifying drugs (DMDs) can significantly reduce relapse rates and disease progression (Fogarty, Schmitz, Tubridy, Walsh, & Barry, 2016). People with MS face a difficult decision when it comes to weighing up the various costs and benefits of DMDs as the complex risk-benefit profiles are not always correctly interpreted and understood by people with MS (Reen, Silber, & Langdon, 2017a).

Additional support may be required when making decisions in these situations as people with MS have been shown to make different decisions in the context of risk (Sepulveda et al., 2017). Under explicit risk conditions, MS patients show greater risk aversion and deficits on tasks which probe the anticipated effects of decision outcomes on future choices (Simioni et al., 2012). This study highlighted that the quality of decision-making under risk was different for MS patients.

It is important that patients are able to understand the complex risk and benefit information surrounding DMDs, which include serious and even fatal side effects, so

that they are better able to make decisions about their treatment. Shared decision-making as part of a patient-centred approach has been advocated as the pinnacle of patient-centred care (Barry & Edgman-Levitan, 2012); patient understanding is a prerequisite for successful shared decision-making. Shared decision-making is associated with better DMD adherence rates in MS, this is critical as the efficacy of DMDs depends on high levels of adherence (Ben-Zacharia et al., 2018).

Reen and colleagues developed a protocol: the Benefit and Risk Information for Medication in Multiple Sclerosis (BRIMMS), in order to improve patients' understanding and certainty about treatment (Reen, Silber, & Langdon, 2017b). The researchers found that the BRIMMS improved patients' understanding and confidence in treatment decisions, compared to standard presentation of treatment information used in the UK.

An individual's risk attitude, risk perception and propensity are important factors that may influence the treatment decision-making process. Once the effect of risk attitude, perception and propensity on treatment understanding and decision certainty is known, characteristics of the patients could be determined in advance of the consultation during which the information is presented. The information could be amended to support the shared decision-making process. A recent systematic review looking at methods to investigate patient preferences for treatment identified the influence of risk perception and uncertainty on treatment decisions as neglected research topics (Webb et al., 2018).

1.2. Systematic Review

The literature suggests that an individual's risk attitude, risk perception and risk propensity may have an impact on decision-making. Interest in this area is justified given that risk information could be used to tailor communication in the shared decision-making process, to accommodate patient risk characteristics.

A systematic review was conducted to investigate MS patients' risk perception, risk attitude, risk tolerance/acceptance and risk knowledge across studies, and consider how this relates to patient treatment decisions.

Online literature databases were systematically reviewed for relevant articles. The inclusion criteria consisted of peer-reviewed studies in English, with human adult patients with any clinical subtype of MS. No date restriction was applied. Studies were required to have a quantitative design. Studies were included if they reported an evaluation related to risk perception, risk attitude, risk tolerance/acceptance or risk knowledge in patients with MS.

Data on participants, study characteristics and key findings were extracted and summarised. A total of 19 studies were included, containing data from 13,054 patients (76% were female), who presented with a range of MS disease subtypes. The mean age of patients ranged from 36.50 years to 55.10 years. Most studies used hypothetical scenarios to assess risk. Two studies included a cognitive measure. Five studies

measured mood using the Hospital Anxiety and Depression. A quality rating tool was used to assess study methodology.

Patients tended to overestimate the short-term risks of MS and underestimate the long-term risks. They had a tendency to rate the general risk as higher than the risk they attribute to themselves. Overall, risk knowledge was low and the results regarding risk attitude were mixed. The more risk-seeking an individual, the more likely they were to choose no treatment. A limitation of the systematic review is the difficulty with which robust conclusions can be drawn, given that the studies used a variety of different methods to assess risk. It could be suggested that a more consistent way of defining and measuring the different elements of risk in MS is required. There was also variation between the studies in terms of study design and patient characteristics. This limits the ability to draw generalisable conclusions and reflects a lack of uniformity across studies that address risk in MS.

1.3. Empirical Study

The primary aim of the study was to confirm the finding that BRIMMS is superior to standard presentation in improving patients' understanding scores and increasing patient certainty in decisions.

Ethical approval was obtained from the Health Research Authority (Reference: 18/NI/0102) and certified by Royal Holloway Research Ethics Committee. The inclusion criteria were: all participants (a) were fluent in English; (b) were aged

between 18 and 65 years; (c) had a diagnosis of Relapsing-Remitting MS (RRMS) by a Consultant Neurologist based on Thompson et al., (2018) criteria; (d) were able to give informed consent; (e) were able to meet the task demands of the experiment in terms of sensorimotor abilities. The exclusion criteria were: (a) significant changes in medication or condition within the last four weeks; (b) a history of significant psychiatric disorders, substance or alcohol abuse; (c) significant medical condition (other than MS), personal or social circumstances that were likely to impact on participating in the study; (d) significant visual, motor or hearing impairments that would have an impact on their engagement with the tests/protocol/questionnaires.

The hypotheses of the study were: (1) the BRIMMS protocol would improve patients' understanding of treatment risks and benefits compared to standard consultation; (2) the BRIMMS protocol would reduce patients' conflict regarding treatment decisions compared to standard consultation; (3) the BRIMMS would be rated more positively by patients than the standard consultation; (4) Self-reported risk attitude (Glanz et al., 2016), perception (Glanz et al., 2016) and propensity to take risks (Bechara, Damasio, Damasio, & Anderson, 1994) would predict patient and patient certainty in treatment decisions.

Participants were provided with a hypothetical clinical trial scenario where the treatment benefits were stipulated for the intervention group (those taking the treatment) and a placebo group (those not taking any treatment). Each patient received treatment risks and benefits presented in both the BRIMMS format, and also standard consultation format as a control condition. Understanding of treatment risks and benefits was

assessed by asking fifteen comprehension questions regarding the side-effects, adverse risks and benefits of each hypothetical treatment. Three feedback questions were asked at the end of each condition. The Decisional Conflict Scale (O'Connor, 1995), a self-reported questionnaire, was used to assess patients' decisional conflicts regarding their treatment options. After being presented with each set of treatments, patients were required to make a decision regarding treatment (i.e. choose one of the two hypothetical treatments, choose neither or say that there were unsure).

Risk was measured by a single-item measure of risk orientation (Maestas & Pollock, 2010), the Risk Propensity Scale (RPS; Meertens & Lion, 2008), a standard gambling scenario (Glanz et al., 2016) and the Iowa Gambling Task (IGT; Bechara, Damasio, Damasio, & Anderson, 1994). Patients were also asked to estimate the likelihood of becoming wheelchair-bound over the short (two years), medium (five years) and long-term (ten years), on a five-point scale (ranging from extremely unlikely to extremely likely).

Some measures and questionnaires were included to benchmark the sample. That is, to ensure that the sample was typical of other published MS samples. Premorbid intellectual functioning was assessed using The Wechsler Test of Adult Reading (WTAR; Wechsler, 2001). Cognition was examined using The Brief International Cognitive Assessment for MS (BICAMS; Langdon et al., 2012). Perceived fatigue was measured by the Fatigue Severity Scale (FSS; Krupp, LaRocca, Muir-Nash, & Steinber, 1989). Self-reported depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983).

The study had a within-subjects design. Using G*Power (Faul, Erdfelder, Lang, & Buchner, 2007) the specified sample size was 46, with an alpha at .05, with a power of .80.

Due to recruitment being slower than expected, 26 participants were recruited. The majority of the sample was female ($n = 19$; 73 %), with a mean age of 43.38 ($SD = 10.32$) and a mean average pre-morbid intelligence quotient (IQ) of 101.65 ($SD = 14.09$). Scores on the HADS were consistent with previously published means for HADS in the MS population (HADS-D: $M = 4.58$, $SD = 3.87$; HADS-A: $M = 7.96$, $SD = 4.40$). Years since diagnosis ranged from 1-26 years ($M = 9.35$, $SD = 6.50$). The average age of diagnosis was 33.70 years, which is in line with previously reported data. Expanded Disability Status Scale (EDSS; Kurtzke, 1983) scores ranged from 0-7 ($M = 2.81$, $SD = 2.45$). 10 (39%) participants were impaired on the Symbol Digit Modalities Test (SDMT), 7 (27%) were impaired on the California Verbal Learning Task II (CVLT-II) and 8 (31%) were impaired on the Brief Visuospatial Memory Test- Revised (BVM-T-R). When comparing the sample means with published norms, the current sample was consistent with previous norms (Bichuetti et al., 2018; Heesen et al., 2017; Orchard, Giovannoni, & Langdon, 2013).

There was support for the first hypothesis that the BRIMMS protocol would improve patients' understanding of treatment risks and benefits compared to standard consultation. An Analysis of variance (ANOVA) showed that there was a significant overall difference between conditions ($F(1, 25) = 3388.83$, $p < .001$), demonstrating

that patients' understanding was significantly higher after the BRIMMS condition ($M = 27.58$; $SD = 1.67$), than after the standard consultation ($M = 3.35$; $SD = 1.29$). However, the effect of condition was non-significant after controlling for depression ($F(1, 22) = .44$, $p = .517$) and fatigue ($F(1, 22) = .35$, $p = .558$).

A repeated measures ANOVA confirmed the second hypothesis that the BRIMMS protocol reduced patients' decisional conflict compared to standard consultation ($F(1, 25) = 10.78$, $p = .003$). Mean score for the BRIMMS was 24.21 ($SD = 14.91$). And mean score for the standard consultation was 38.28 ($SD = 17.32$). The third hypothesis that the BRIMMS would be rated more positively by patients than the standard consultation was not supported. A repeated measures ANOVA revealed no significant effect of consultation on patient feedback ($F(1, 25) = .94$, $p = .339$). Mean score for the BRIMMS was 7.22 ($SD = 2.07$) and mean score for the standard consultation was 6.55 ($SD = 2.59$).

There was no evidence for the fourth and fifth hypotheses regarding associations between self-reported risk attitude, perception, propensity to take risks and understanding or decisional conflict.

Several limitations were noted. Firstly, the use of hypothetical disease and treatments raises the possibility that the findings may not apply to the understanding of real DMD risks and benefits, in that the information was not personally relevant. The study could have benefited from a more robust design where each patient receives two different hypothetical diseases, each with two different hypothetical treatments.

In summary, the BRIMMS is associated with better patient understanding of treatment risks and benefits and reduced decisional conflict, compared to standard consultation. However, differences in understanding scores may be explained by either fatigue or depression. It is recommended that the BRIMMS should be further evaluated and implemented in real consultation in a clinical setting.

1.4. Integration, Impact and Dissemination

The integration of the two components serves to provide a narrative around the need for patients to understand the risks and benefits associated with the DMDs, in order to approve adherence. The thesis is well linked to various government notes ("*PN 500*", 2017), reports (*The Academy of Medical Sciences*, 2017) and international initiatives (Rieckmann et al., 2018). These sources stipulate that effective communication of the evidence regarding the benefits, risks and uncertainty of treatments in a way that is clear, accessible and usable so that patients can make sense of it is a key priority for research. The results of the systematic review demonstrate that patients tend to overestimate the short-term risks of the disease and underestimate the long-term risks. MS patients have a tendency to rate the general risk as higher than the risk they attribute to themselves. The more risk-seeking an individual, the more likely they are to choose no treatment. The findings of the empirical study suggest that the BRIMMS is a tool that could be used in order to improve the shared decision-making process around DMDs.

2. Systematic Review

What do Multiple Sclerosis patients perceive about the risks of Multiple Sclerosis:

A systematic review

2.1. Abstract

Multiple Sclerosis (MS) is a chronic inflammatory disorder of the central nervous system, which often results in neurological disability. Disease modifying drugs have the potential to reduce the number of relapses and delay the progression of the disease. The different and complex risk-benefit profiles of the drugs need to be effectively communicated to people with MS, which is not always achieved. Additional support may be required when making decisions in these situations as people with MS have been shown to make different decisions in the context of risk. Under explicit risk conditions, MS patients show a greater risk aversion and deficits on tasks which probe the anticipated effects of decision outcomes on future choices. The aim of this systematic review was to evaluate MS patient's risk perception, risk attitude, risk tolerance/acceptance and risk knowledge across studies, and consider how this relates to patient treatment decisions. A literature search was performed in PubMed, Web of Science and PsycINFO in March 2019. The Effective Public Health Practice Project quality assessment tool for quantitative studies was used to examine the quality of the studies. 19 studies met the inclusion criteria. Data from

13,054 MS patients were included in the review. The results showed that patients overestimate the benefits of treatment, overall risk knowledge is low and the results regarding risk attitude are mixed. The more risk-seeking an individual the more likely they are to choose no treatment. Overall, a greater understanding of a patients' risk profile (risk perception, risk attitude, risk knowledge and risk tolerance/acceptance) is important for shared decision-making. Taking this information into account could lead to greater satisfaction with treatment choice and greater adherence. It might be possible to assess patients on a variety of risk variables and tailor communication to support and accommodate their particular risk profile.

2.2. Introduction

Multiple Sclerosis (MS) affects approximately 2.3 million people worldwide (Thompson, Baranzini, Geurts, Hemmer, & Ciccarelli, 2018). MS is a chronic inflammatory disorder of the central nervous system, which often results in neurological disability (Dutta & Trapp, 2014). The condition causes changes in sensation, mobility, balance, sphincter activity, vision and cognition (Brownlee, Hardy, Fazekas, & Miller, 2017).

Most people with MS initially experience Relapsing Remitting MS (RRMS) followed by Secondary Progressive MS (SPMS), the latter is a disease course characterised by disability progression, with more frequent exacerbations with little or no improvement (Stadelmann, Wegner, & Bruck, 2011). It has been suggested that the switch from RRMS to SPMS occurs about 10-15 years after onset (Leray et al., 2010; Scalfari et al.,

2010). Disability associated with SPMS affects various functions such as gait, balance, vision, cognition and continence (Rovaris et al., 2006). The most common functional consequence of MS is mobility problems. This affects 50% of those diagnosed within 15 years of disease onset (Noseworthy, Lucchinetti, Rodriguez, & Weinshenker, 2000). For those with RRMS, the median time from diagnosis to requiring a wheelchair for mobility is 28 years (Scalfari et al., 2010). This first attack of MS is referred to as a clinically isolated syndrome (CIS). However, some patients present with a gradual progressive course without a clearly defined initial attack; this is termed Primary Progressive MS (PPMS). The least common type of MS is Progressive Relapsing MS (PRMS), which is characterised by a gradually worsening state from the start, with acute relapses.

Disease modifying drugs (DMDs) have the potential to reduce the number of relapses and delay the progression of the disease (Vargas & Tyor, 2017). The treatments that MS patients are often initially offered, first-line DMDs, have good long-term safety profiles and limited adverse risks, however they are only moderately successful (Auricchio et al., 2017). If the initial treatments are not effective, or the disease is aggressive from the start, second-line DMDs may be offered. These DMDs have higher efficacy, but potentially more frequent serious adverse effects, including leukemia, cardiotoxicity, and progressive multifocal leukoencephalopathy (Torkildsen, Myhr, & Bo, 2016).

The different and complex risk-benefit profiles of the drugs need to be effectively communicated to people with MS, which is not always achieved (Reen, Silber, & Langdon, 2017a). Shared decision-making in health care is accepted as the optimal

approach for treatment decisions (Elwyn et al., 2012; Barry, 2012). Additional support may be required when making decisions in these situations as people with MS have been shown to make different decisions in the context of risk (Sepulveda et al., 2017).

Some decisions are made in situations that offer explicit information about the possible consequences of making a certain decision, therefore requiring people to choose between the alternative concrete options, which are associated with different rewards and punishments (Simioni et al., 2012). Under these explicit risk conditions, MS patients show a greater risk aversion and deficits on tasks which probe the anticipated effects of decision outcomes on future choices (Simioni et al., 2012). Patients also differed from controls in the quality of their decision-making on a gambling task; they selected the most favourable odds less often than controls and also had longer deliberation times before choosing an option. This study highlighted that the quality of decision-making under risk was different for MS patients.

An individual's risk perception, risk attitude/risk propensity, risk knowledge and risk tolerance/acceptance are important characteristics that may influence their treatment decisions. "Risk perception" is defined as one's subjective judgments and interpretation about risk, e.g. about the likelihood of negative outcomes such as illness, injury and death (Paek & Hove, 2017). Risk perception is a very individual assessment and is likely to be affected by personal experience. Disease risk perceptions are critical in determining health behaviour (Ferrer & Klein, 2015). "Risk attitude" is a construct that characterizes an individual's decision-making in terms of taking or avoiding risk when deciding how to proceed under conditions of uncertainty (Rosen, Tsai, & Downs, 2003).

The term “risk propensity” is often used in the same way to describe an individual’s current tendency to take or avoid risk (Sitkin & Weingart, 1995). Risk attitude/risk propensity are explicitly estimated of a behaviour or risk-related action. “Risk knowledge” in the context of medical decision-making refers to the determinants, inheritance, prognosis and the risks and benefits of treatments (Gigerenzer & Gray, 2013). Risk knowledge refers to known or understood information (factual and detailed), which is less likely to be influenced by personal experience and emotion. An additional relevant characteristic is individual willingness to accept certain risks associated with treatments: “risk tolerance or acceptance”. This gives a detailed estimate of risks that would be taken as a result of certain behaviours or actions (treatment choice), but this time in the context of a treatment benefit. Something bad is going to happen (illness related), therefore the risks of treatment are weighed against treatment benefit. Doing nothing has a cost in this instance.

Some researchers have argued that the concept of risk perception is complex and vague. They have suggested that instead, it should be collectively termed “risk judgment” because this includes cognitive, affective, and behavioural dimensions as well as perceptual elements (Dunwoody & Neuwirth, 1991). The emphasis on the rational and cognitive aspects of risk perceptions can be seen in health behaviour theories such as the Health Behaviour Model (HBM). The HBM is based on the assumption that people want to avoid illness and will therefore engage behaviours which they believe will protect them from illness (Paek & Hove, 2017). The HBM includes four categories of risk perception, which are thought to be precursors to health behaviour: perceived

susceptibility, perceived severity, perceived benefits, and perceived barriers (Paek & Hove, 2017). “Perceived susceptibility” refers to people’s subjective beliefs regarding their vulnerability and how susceptible they are to a disease/other health risk. The model also includes “perceived severity”: how serious one believes a health risk is, and whether the risk would result in adverse consequences such as ostracism, stigma, and shame. “Perceived benefits” refers to beliefs about whether health behaviours will manage health risks. “Perceived barriers” refers to one’s beliefs about the costs or negative aspects of engaging in a health behaviour and whether these will prevent one doing so (Peak & Hove, 2017).

Some researchers have argued that more dimensions of risk perception need to be explored. A meta-analysis suggests including “perceived likelihood”, which refers to the probability that one will be harmed by a risk (Brewer, Chapman, Gibbons, & McCaul, 2007). The authors reviewed 34 studies and “perceived likelihood” seemed to be a distinct component of risk perception, which was consistently related to health behaviour. In addition, it is important to note that there is often a difference between patients and healthcare professionals regarding perceived acceptable DMD risks (Kremer, Evers, Jongen, & Hiligsmann, 2018).

Over the last decade, several oral and monoclonal antibody therapies have been licenced for MS (See Figure 1). DMDs are only effective in the relapsing forms of MS, with the exception of Ocrelizumab (licenced for PPMS) and Siponimod (licenced for SPMS). The mechanisms of how DMDs work are not fully understood. It is thought that by constraining the dysregulated immune system, DMDs may limit the inflammation of the

nervous system, preventing relapses and new inflammatory lesions (De Angelis, John, & Brownlee, 2018).

Natalizumab, a monoclonal antibody, is one of the most effective treatments currently available for RRMS (Yaldizli & Putzki, 2009). Monthly intravenous injections are generally well tolerated, with the exception of rare hypersensitivity reactions (O'Connor et al., 2014). Natalizumab is associated with an increased risk of developing progressive multifocal leukoencephalopathy (PML). PML is an opportunistic, disabling and potentially life-threatening disease caused by the John Cunningham Virus (JCV). Prior to commencing treatment, all patients should be screened for previous JCV infection. The estimated risk for PML in JCV-negative patients is low (0.1/1000; Pavlovic, Patera, Nyberg, Gerber, & Liu, 2015). Amongst JCV-positive patients, the risk of developing PML is influenced by the treatment duration and previous immunosuppressive treatment. Risk is relatively low during the first two years of treatment and increases thereafter. Patients are monitored throughout treatment for JCV, PML and other safety considerations (Clerico et al., 2017).

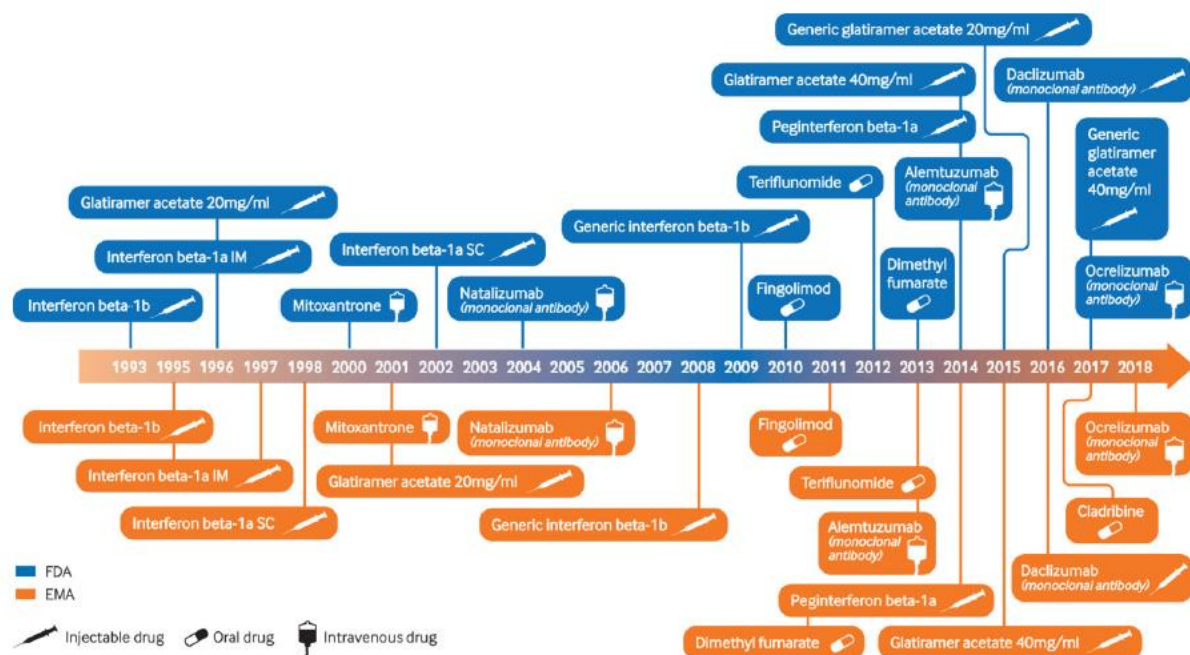


Figure 1. Timeline depicting the approval of DMDs for MS by the Food and Drug Administration and the European Medicine Agency. Reprinted from “Disease-modifying therapies for multiple sclerosis”, by F. De Angelis, N. John and W. Brownlee, 2018, *BMJ*, 363, p. 10.

Mitoxantrone is rarely used in MS and is administered via infusion, which is usually repeated once every three months for two years and is generally well tolerated in patients with MS. The short-term most frequent adverse events documented have been nausea/vomiting (62%), alopecia (47%) and increased risk of infection, mostly urinary tract infections (25%) and respiratory tract infections (35%), especially in patients with little mobility (Martinelli, Radaelli, Straffi, Rodegher, & Comi, 2009). The most serious risks of are cardiotoxicity and therapy-related acute leukaemia (TRAL). Cardiotoxicity is present in 0.25-0.50% of patients and has been found to be related to dosage (Ghalie, et al., 2002). In order to minimise this risk, patients receive cardiac function testing

every six months. A review of the literature found that TRAL was diagnosed in 0.73% of the 12,896 patients identified (Ellis, Brown, & Boggild, 2015).

Patients with MS are challenged making decisions under risk conditions. They present with an atypical profile when it comes to health risk. These aspects might have an influence on how well they are able to simulate and process risk information that they are given about DMDs, because it is known that the different and complex risk-benefit profiles of the drugs are not always correctly understood by patients with MS (Reen et al., 2017a).

There are several aspects of risk that could affect how MS patients perceive and manage their illness. Firstly, risk directly related to disease process and secondly in relation to risk of DMDs. There is also a question regarding how individual or group characteristics may influence this (risk attitude/risk tolerance).

Research questions:

- 1) How do patients with MS perceive the risk of MS severity?
- 2) How do patients with MS perceive the risk of wheelchair dependency?
- 3) How do patients with MS perceive the risks of DMD treatment?
- 4) What is risk attitude of patients with MS?
- 5) What is risk knowledge of patients with MS?
- 6) What is risk tolerance/acceptance of patients with MS?

The literature suggests that an individual's risk attitude, perception and propensity may

have an impact on decision-making. Interest in this area is justified because risk information could be used to tailor communication which facilitates shared decision making, to accommodate patient risk characteristics.

To the best of our knowledge, the present review is the first with the primary aim of evaluating MS patients' risk perception, risk attitude, risk tolerance/acceptance and risk knowledge across studies, and to consider how this relates to patient treatment decisions.

2.3. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations were used as a guide for the reporting of information in this review (Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009). A protocol for the present review was not previously published or registered.

2.3.1. Systematic literature search

The systematic literature search was conducted in March 2019 using PubMed, Web of Science and PsycINFO using specific search terms (See Table 1). After removing duplicate studies, a total of 118 records were identified (See Figure 2).

Table 1

Search terms for systematic review

(Multiple AND sclerosis)

AND

(Patients OR patient OR persons OR people OR individuals OR individual

AND

(Risk perception OR risk attitude OR risk knowledge OR risk propensity OR risk attitudes
OR risk perceptions OR perception of risk OR risk tolerance OR risk acceptance)

2.3.2. Eligibility criteria

The inclusion criteria consisted of peer-reviewed studies in English, with human adult patients with any clinical subtype of MS. No date restriction was applied. Studies were required to have a quantitative design. Qualitative studies were not included in this review due to the potential epistemological differences between qualitative and quantitative research, which suggests that they warrant separate synthesis. Studies were included if they included an evaluation related to risk perception, risk attitude, risk

tolerance/acceptance or risk knowledge in patients with MS. All titles and abstracts were screened. At this stage, 19 studies were considered for eligibility and full texts were accessed.

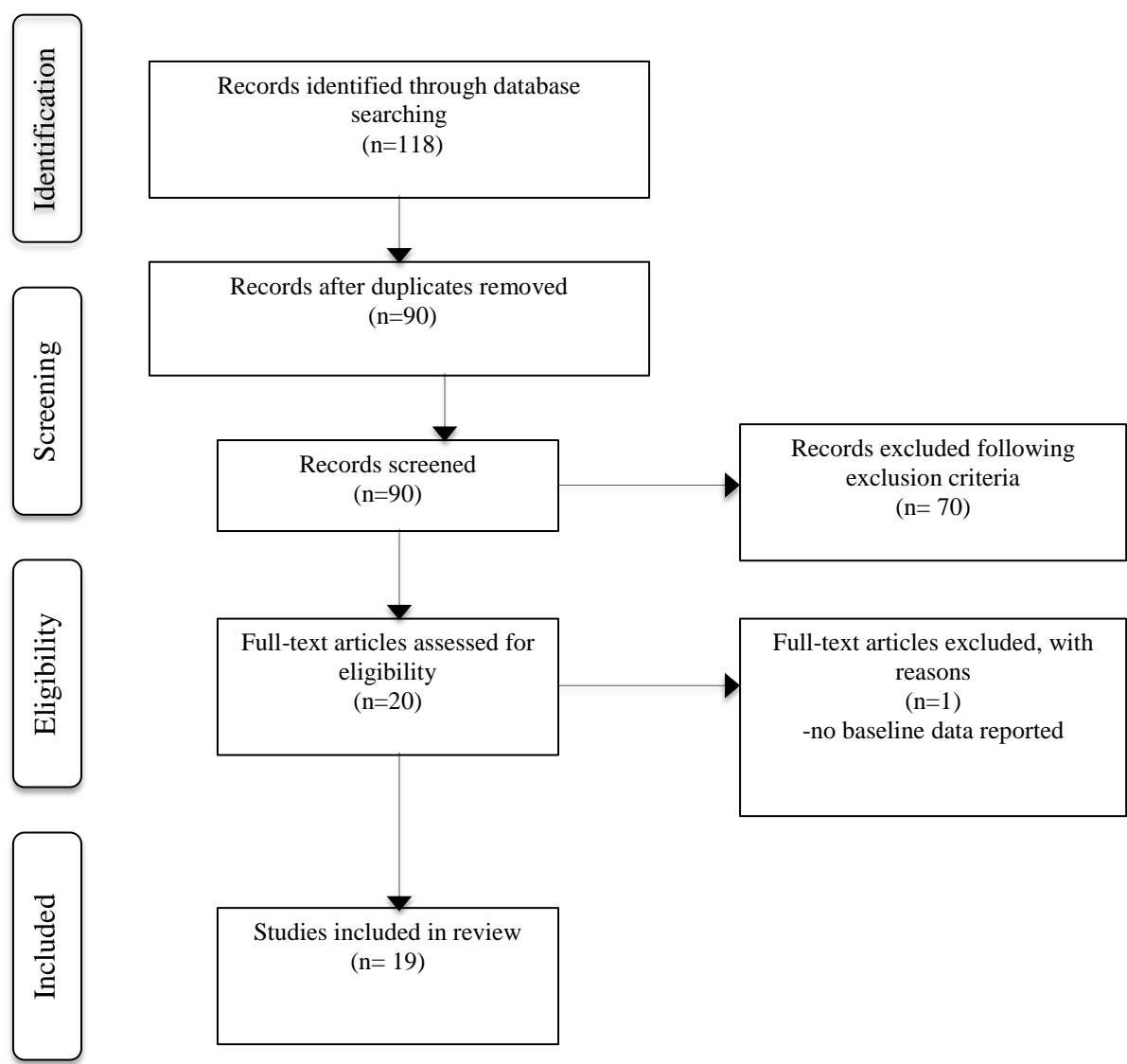


Figure 2. PRISMA flow chart for selection process of studies.

2.3.3. Data extraction

Data extraction forms were created to extract relevant information from the full texts, and assess their eligibility for the final review. Extraction was carried out by one reviewer (ED) and verified by another (DL). Any discrepancies were resolved by discussion. Following data extraction, 70 studies were excluded from the final review due to the exclusion criteria.

Baseline characteristics of MS patients were extracted from the shortlisted studies (See Table 2). This included (where reported) age, gender, type of MS, disease duration, time since diagnosis and The Expanded Disability Status Scale (EDSS; Kurtzke, 1983) and Patient Determined Disease Steps (PDDS; Hohol, Orva, & Weiner, 1995). Information was recorded regarding whether or not the study had a control group, as well as any cognitive measures undertaken by the patients (including measures of mood). Any data available on assessing risk perception, risk attitude, risk tolerance/acceptance and risk knowledge of patients was retained, including how risk was measured and the outcome of such studies.

2.3.4. Quality assessment

The Effective Public Health Practice Project (EPHPP) quality assessment tool for quantitative studies was used to examine the quality of the studies (Thomas, Ciliska, Dobbins, & Micucci, 2004). The EPHPP tool was chosen because it is often used to evaluate studies in a health care setting, it has a high inter-rater reliability (Armijo-

Olivo, Stiles, Hagen, Biondo, & Cummings, 2012) and is considered useful when conducting a systematic review (Deeks et al., 2003). The final quality rating was based on selection bias, study design, confounders, blinding, data collection method, and withdrawals and drop-outs (See Table 3).

2.4. Results

2.4.1. Study design and participant demographics

19 studies were identified in the review, most of which used a questionnaire design. Control data was collected in five of the studies (Prosser & Wittenberg, 2007; Tur et al., 2013; Kopke et al., 2014; Bsteh et al., 2017; Kopke et al., 2017). Two of the nineteen studies were considered to be of a strong quality, with three studies considered to be of a moderate quality and the remaining fourteen studies were considered to be of a weak quality according to the EPHPP Quality Assessment Tool. It is important to use the EPHPP as a standardised means to assess study quality.

Across the 19 studies, a total of 13,054 MS patients were included with a range of MS disease subtypes: 0.30% (45) CIS patients, 38% (4,992) RRMS patients, 3% (368) SPMS patients, 1.50% (191) PPMS patients and 0.10% (7) PRMS patients. The remaining 57% of patients had unclear or unreported MS disease subtype. The mean age of patients ranged from 36.50 to 55.10 years. One study stated the median age as 40 years (Kopke et al., 2014). Of the 13,054 patients, 76% (9,934) were female and 23%

(3,024) were male. One study including 1% (96) of the total patients did not specify gender (Bichuetti et al., 2018).

Five studies reported time since first symptom (Janssens et al., 2003; Janssens et al., 2004; Kopke et al., 2014; Glanz et al., 2016; Heesen et al., 2017) with a range from 3.70 years to 15.50 years. 16 studies reported patients' mean time since diagnosis (Janssens et al., 2003; Janssens et al., 2004; Heesen, Kasper, Segal, Köpke, & Mühlhauser, 2004; Heesen et al., 2010; Hofmann et al., 2012; Tur et al., 2013; Kopke et al., 2014; Fox et al., 2015; Kopke et al., 2017; Bichuetti et al., 2018; Bsteh et al., 2017; Heesen et al., 2017; Bruce et al., 2018a; Bruce et al., 2018b; Giordano et al., 2018; Fox et al., 2019) with a range from 7.80 months to 16.60 years. Two studies did not specify either time since first symptom or time since diagnosis (Prosser, Kuntz, Bar-Or, & Weinstein, 2002; Prosser et al., 2007). Four studies gave both time since diagnosis and time since first symptom (Janssens et al., 2003; Janssens et al., 2004; Kopke et al., 2014; Heesen et al., 2017).

11 of the 19 studies reported an EDSS, a measure of neurological disability, five reported the mean EDSS and six reported the median EDSS. The median EDSS ranged from 1.50 (no disability, minimal signs in more than one functional system) to 4.00 (significant disability but self-sufficient and up and about some 12 hours a day and able to walk without aid or rest for 500m; Janssens et al., 2003; Janssens et al., 2004; Heesen et al., 2010; Tur et al., 2013; Glanz et al., 2016; Bsteh et al., 2017). The mean EDSS ranged from 2.60 (mild disability in one functional system or minimal disability in two functional systems) to 3.70 (moderate disability in one functional system and more than

minimal disability in several others and no impairment to walking; Prosser et al., 2002; Prosser et al., 2007; Bichueti et al., 2018; Heesen et al., 2017; Kopke et al., 2017). Four studies reported PDDS score, which is a self-reported outcome measure used in MS that strongly correlates with the EDSS (Learmonth, Moti, Sandroff, & Cadavid, 2013). Scores on the PDDS vary from 0 (normal) to 8 (bedridden). Three studies reported the mean, ranging from 1.67 (which corresponds to mild/moderate disability with limited gait abnormality) to 3.20 (which corresponds to gait disability, occasionally requiring assistance to walk; Fox et al., 2015; Bruce et al., 2018a; Bruce et al., 2018b). One study reported the median PDDS as 3 (Fox et al., 2019).

Two studies included a cognitive measure (Heesen et al., 2017; Bruce et al., 2018b). Patients were assessed on the Symbol Digit Modalities Test (SDMT), a test of information processing speed and data was available for 441 of the 801 patients. 35% of patients were considered to have a cognitive deficit (as indicated by a test results 1.50 standard deviations below that of an age matched control group; Heesen et al., 2017). Bruce et al., (2018b) created a cognitive composite score by using SDMT, The Rey Auditory Learning Test (verbal learning) and Trails B (executive skills). Higher score represent better cognitive functioning. Mean cognitive composite score was -0.0018 (SD=0.77; range -3.26 to 1.65). The authors reported that only two patients scored below -2, indicating cognitive impairment.

One study included the Beck Depression Inventory-II (BDI-II; Beck, Steer & Brown, 1996) as a screen for symptoms of depression; four patients had a score ≥ 18 indicating a clinical level of depression (Bsteh et al., 2017). Qualitatively, these patients also

reported higher burden of disease and a stronger subjective loss of health. Depressed patients did not differ significantly from patients without depression in terms of risk behaviour. Four studies measured mood using the HADS (Janssens et al., 2004; Kopke et al., 2014; Kopke et al., 2017; Bruce et al., 2018b). Patients with higher disability reported significantly more symptoms of anxiety and depression. 34% of patients had clinically relevant levels of anxiety and 10% of depression (>8 on HADS; Janssens et al., 2004). Mean scores on the HADS were low at baseline (Anxiety = 7.00 ± 3.60 for the intervention group and 7.00 ± 3.70 for the control group; Depression = 4.10 ± 3.80 for the intervention group and 4.80 ± 4.10 for the control group; Kopke et al., 2014). Bruce et al. (2018b) reported slightly higher rates with a mean overall score of 11.62 on the HADS. Disease related distress was measured by the Impact of Events Scale (IES; Horowitz, Wilner, & Alvarez, 1979) in one study (Janssens et al., 2004). Patients with more disability were significantly more distressed, researchers found a positive correlation between EDSS and intrusion and avoidance on the IES.

The studies identified examined different aspects of risk in MS. In order to compare and critique, the studies were grouped as follows: firstly, risk perception of disease and disability (perceived risk of disease severity/perceived risk of wheelchair dependency); secondly, risk perception of DMD treatment; thirdly, risk knowledge and fourthly, individual risk tolerance/acceptance.

Table 2
Study design and patient demographics

Study (first author, year)	Quality Rating	Methodological design IG=Intervention group CG=Control group	Recruitment method	Sample size	Gender (n) Female=F Male=M	Age in years	Type of MS (n) CIS=Clinically Isolated Syndrome RRMS=Relapsing-Remitting MS SPMS=Secondary-Progressive MS PPMS=Primary-Progressive MS PRMS=Progressive-Relapsing MS	Time since first symptom	Time since diagnosis	EDSS score unless stated otherwise	On treatment
Prosser, 2002	Weak	Survey	MS clinic over a 6 month period	56	44 (F) 12 (M)	38.00 (mean)	RRMS (56)	-	-	3.70 (mean)	33
Janssens, 2003	Weak	Questionnaire and interview	MS clinic	101	70 (F) 31 (M)	37.50 (mean)	Unspecified (101)	3.70 years (mean)	7.80 months (mean)	2.50 (median)	-
Janssens, 2004	Weak	Questionnaire	MS clinic	101	70 (F) 31 (M)	37.50 (mean)	Unspecified (101)	3.70years (mean)	7.80 months (mean)	2.50 (median)	-
Heesen, 2004	Moderate	Postal questionnaire-observational study	Randomly selected from outpatient register	169	106 (F) 63 (M)	44.00 (mean)	RRMS (75); PPMS (75); Unspecified (19)	-	7.70 years (mean)	-	103

Study (first author, year)	Quality Rating	Methodological design IG=Intervention group CG=Control group	Recruitment method	Sample size	Gender (n) Female=F Male=M	Age in years	Type of MS (n) CIS=Clinically Isolated Syndrome RRMS=Relapsing-Remitting MS SPMS=Secondary-Progressive MS PPMS=Primary-Progressive MS PRMS=Progressive-Relapsing MS	Time since first symptom	Time since diagnosis	EDSS score unless stated otherwise	On treatment
Prosser, 2007	Weak	Survey and control group	MS clinic and residents in San Diego	56	44 (F) 12 (M)	38.00 (mean)	RRMS (56)	-	-	3.70 (mean)	-
Heesen, 2010	Moderate	Questionnaire	MS clinic	69	45 (F) 24 (M)	40 .00 (median)	Unspecified (69)	-	11.00 years (median)	4.00 (median)	64
Hofmann, 2012	Weak	Retrospective cohort study	Database from university medical centre, hospitals and one private practice	575	371 (F) 204 (M)	50.30 (mean)	RRMS (49); SPMS (258); PPMS (76); Other/unknown (192)	-	14.30 years (median)	-	53

Study (first author, year)	Quality Rating	Methodological design IG=Intervention group CG=Control group	Recruitment method	Sample size	Gender (n) Female=F Male=M	Age in years	Type of MS (n) CIS=Clinically Isolated Syndrome RRMS=Relapsing-Remitting MS SPMS=Secondary-Progressive MS PPMS=Primary-Progressive MS PRMS=Progressive-Relapsing MS	Time since first symptom	Time since diagnosis	EDSS score unless stated otherwise	On treatment
Tur, 2013	Weak	Survey Natalizumab treated (IG) Other DMD (CG)	MS centre	136	IG 80 (F) 34 (M) CG 16(F) 6 (M)	IG 37.78 (mean) CG 39.16 (mean)	-	-	IG 12.92 (mean) CG 5.21 (mean)	IG 3.75 (median) CG 2.00 (median)	136
Kopke, 2014	Strong	12 m, 6 centre, double-blind RCT Baseline data. 4hr interactive education (IG) vs stress management (CG)	MS clinic	192	IG 69 (F) 24 (M) CG 74(F) 25(M)	IG 36.50 (mean) CG 36.70 (mean)	CIS (27); RRMS (133); Unclear (32)	IG (4.30 years; mean) CG (4.00 years; mean)	IG (1.40 years; mean) CG (1.20 years; mean)	-	41 (IG) 45 (CG)
Fox, 2015	Weak	Questionnaire	MS registry	5446	4250 (F) 1196 (M)	52.70 (mean)	-	-	13.90 (mean)	3.20 (mean-PDDS)	3700

Study (first author, year)	Quality Rating	Methodological design IG=Intervention group CG=Control group	Recruitment method	Sample size	Gender (n) Female=F Male=M	Age in years	Type of MS (n) CIS=Clinically Isolated Syndrome RRMS=Relapsing-Remitting MS SPMS=Secondary-Progressive MS PPMS=Primary-Progressive MS PRMS=Progressive-Relapsing MS	Time since first symptom	Time since diagnosis	EDSS score unless stated otherwise	On treatment
Glanz, 2016	Weak	Questionnaire	MS centre	223	173 (F) 50 (M)	49.30 (mean)	CIS (13); RRMS (158); SPMS (44); PPMS (5); PRMS (3)	15.50 years (mean)	-	1.50 (median)	165
Bichuetti, 2018	Weak	Questionnaire	MS clinic	96	Did not specify	39.30 (mean)	RRMS (96)	-	9.10 years (mean)	2.60 (mean)	94
Bsteh, 2017	Weak	Questionnaire compared to published norms.	MS clinic	22	15 (F) 7 (M)	42.30 (mean)	RRMS (17); SPMS (3); PPMS (2)	-	9.00 years (mean)	2.50 (median)	16
Heesen, 2017	Moderate	Multi-centre non-interventional observational study.	MS clinic and private practice	801	562 (F) 239 (M)	38.60 (mean)	RRMS (801)	10.20 years (mean)	8.70 years (mean)	3.10 (mean)	801

Study (first author, year)	Quality Rating	Methodological design IG=Intervention group CG=Control group	Recruitment method	Sample size	Gender (n) Female=F Male=M	Age in years	Type of MS (n) CIS=Clinically Isolated Syndrome RRMS=Relapsing-Remitting MS SPMS=Secondary-Progressive MS PPMS=Primary-Progressive MS PRMS=Progressive-Relapsing MS	Time since first symptom	Time since diagnosis	EDSS score unless stated otherwise	On treatment
Kopke, 2017	Strong	Controlled rater-blinded. Two cohorts separated by time (2months). CG=standard care. IG =patient information programme	Neurological rehabilitation centres	156	IG 62 (F) 13(M) CG 55(F) 26(M)	IG (42.20; mean) CG (42.50; mean)	CIS (5); RRMS (105); SPMS (14); PPMS (13); Other/unknown (19)	-	IG (7.00 years; mean) CG (9 .00 years; mean)	IG 3.30 (mean) CG 3.40 (mean)	40 (IG) 48 (CG)
Bruce, 2018a	Weak	Questionnaire	MS clinic, online, letters and MS newsletter	290	232 (F) 58 (M)	49.28 (mean)	RRMS (217) SPMS (49) PPMS (20) PRMS (4)	-	11.97 years (mean)	2.40 (mean PDDS)	190
Bruce, 2018b	Weak	Questionnaire	MS clinic, via advertisements and via MS newsletter	208	173 (F) 35 (M)	46.02 (mean)	RRMS 208	-	11.00 years (mean)	1.67 (mean PDDS)	167

Study (first author, year)	Quality Rating	Methodological design IG=Intervention group CG=Control group	Recruitment method	Sample size	Gender (n) Female=F Male=M	Age in years	Type of MS (n) CIS=Clinically Isolated Syndrome RRMS=Relapsing-Remitting MS SPMS=Secondary-Progressive MS PPMS=Primary-Progressive MS PRMS=Progressive-Relapsing MS	Time since first symptom	Time since diagnosis	EDSS score unless stated otherwise	On treatment
Giordano, 2018	Weak	Survey (in 8 countries)	Online	986	755 (F) 231 (M)	38.60 (mean)	RRMS (986)	-	7.80 years (mean)	-	-
Fox, 2019	Weak	Survey	MS registry	3371	2668 (F) 703 (M)	55.10 (mean)	RRMS (2035) Other (1331)	-	16.60 years (mean)	3.00 (median PDDS)	1798
TOTAL				13,054	9934(F) 3024(M) 96 (Did not specify)		CIS (45) RRMS (4992) SPMS (368) PPMS (191) PRMS (7) Other/unknown (7451)				

Table 3

Quality assessment of studies that have included measures of risk in MS patients

Study (first author, year)	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropout	Overall quality rating
Prosser, 2002	Moderate	Weak	Weak	Weak	Weak	N/A	Weak
Janssens, 2003	Moderate	Weak	Weak	Weak	Moderate	N/A	Weak
Janssens, 2004	Moderate	Weak	Weak	Weak	Moderate	N/A	Weak
Heesen, 2004	Moderate	Weak	Weak	Moderate	Strong	Moderate	Moderate
Prosser, 2007	Moderate	Weak	Weak	Weak	Weak	N/A	Weak
Heesen, 2010	Moderate	Moderate	Moderate	Weak	Moderate	N/A	Moderate
Hofmann, 2012	Weak	Moderate	Weak	Moderate	Weak	Weak	Weak
Tur, 2013	Moderate	Strong	Moderate	Weak	Weak	N/A	Weak
Kopke, 2014	Strong	Strong	Strong	Strong	Strong	Strong	Strong
Fox, 2015	Moderate	Weak	Weak	Weak	Weak	N/A	Weak
Glanz, 2016	Moderate	Weak	Weak	Weak	Moderate	N/A	Weak
Bichuetti, 2018	Moderate	Weak	Weak	Weak	Moderate	N/A	Weak
Bsteh, 2017	Moderate	Weak	Weak	Weak	Strong	N/A	Weak
Heesen, 2017	Moderate	Moderate	Moderate	Weak	Moderate	N/A	Moderate
Kopke, 2017	Moderate	Strong	Strong	Moderate	Strong	Strong	Strong
Bruce, 2018a	Moderate	Weak	Weak	Weak	Moderate	N/A	Weak
Bruce, 2018b	Moderate	Weak	Weak	Weak	Moderate	N/A	Weak
Giordano, 2018	Moderate	Weak	Weak	Weak	Moderate	N/A	Weak
Fox, 2019	Moderate	Weak	Weak	Weak	Weak	N/A	Weak

Overall quality rating: Strong=no weak ratings; Moderate=one weak rating; Weak=two or more weak ratings.

2.4.2. Risk perception

Risk perception refers to one's subjective judgments and interpretation about risk, e.g. the likelihood of negative outcomes such as illness, injury and death (Paek & Hove, 2017).

2.4.2.1 Risk perception of disease severity

Perceived risk of severity of MS was assessed in four studies (Heesen et al., 2010; Tur et al., 2013; Heesen et al., 2017; Bichuetti et al., 2018) using a visual analogue scale (VAS). A VAS is a commonly used method to measure subjective experience of constructs such as pain, fatigue and anxiety. A VAS is usually presented as a single 100mm line with anchor words at each end of the scale (e.g. no pain-worst imaginable pain). The VAS does not have gradations and is considered to be more sensitive than scales with intermediate marks; patients are not bound to predefined categories, but rather given the opportunity to place themselves at one point along a continuum (Hjermstad et al., 2011). A number of studies have suggested that a VAS is a reliable and valid technique (Remington, Tyrer, Newson-Smith, & Cicchetti, 1979; Hasson & Arnetz, 2005).

Patients were asked to rate the extent to which they perceived MS to be a severe disease (See Table 4). Patients considered their own disease to be less severe than they rated MS risk for patients in general (Tur et al., 2013). Broadly similar predictive variables within a multiple regression model were sex, age and EDSS. Men rated MS as more

severe ($\beta = -0.10$, $p = 0.02$), the perception of severity increased with age ($\beta = 0.10$, $p = 0.02$), as well as with increased disability ($\beta = 0.13$, $p = 0.00$; Heesen et al., 2017).

Table 4

Risk perception of disease severity

Study	VAS design	Mean IG	Mean CG	SD	Median	Interquartile range
Heesen, 2010	Range 0-10 ^a	-		-	8.50	6.50-9.50
Tur, 2013	Range 0-10	7.00 (general) 5.77 (individual) ^b	7.62 (general) 6.10 (individual)	-	-	-
Bichuetti, 2018	Range 0-10	7.30		+/-2.40	-	-
Heesen, 2017	Range 1-25 ^c	18.60		-	-	-

Note. SD=Standard Deviation. IG=Intervention Group. CG=Control Group

^a0=MS is not at all a severe disease; 10=MS is the most severe disease you can think of

^bTwo scores were obtained, one in general (for MS patients as a whole) and one for individual (in their particular case)

^c1=benign; 25=severe.

Whilst all three studies yielded similar results, a possible disadvantage of using a VAS is that patients may have difficulty finding the point that is most applicable to them (Duncan, Bushnell, & Lavigne, 1989).

2.4.2.2. Perceived risk and perceived seriousness of wheelchair dependency

The course of MS is largely unpredictable and uncertain, with serious consequences, such as wheelchair dependency. Patients' perceived risk of wheelchair dependency was assessed using a VAS (Janssens et al., 2003; Janssens et al., 2004) and a 5-point scale (Glanz et al., 2016). Patients' perceived seriousness of becoming wheelchair dependent was assessed using a VAS (Janssens et al., 2003). Patients rated seriousness of wheelchair dependency after two years, ten years and for a lifetime, with the VAS points anchored at 'not serious at all (0)' and 'the most serious thing I can imagine' (100). Wheelchair dependency was defined as the inability to walk more than five metres. Likelihood and seriousness of each patients' wheelchair dependency was measured on a VAS over the short (two years), medium (ten years) and long-term (lifetime; Janssens et al., 2003), with its points anchored at 'definitely not (0%)' and 'definitely (100%)'. Actual risks were derived from epidemiological data and estimated to be 5-10% for two year risk, 20-25% for ten year risk and 70-80% for lifetime risk (Weinsheker, 1989). Glanz et al. (2016) asked patients to estimate the likelihood that they would become wheelchair dependent in two years (short), five years (medium) and

ten years (long-term) on a five point scale, ranging from extremely unlikely to extremely likely.

When compared to the epidemiological data (data based on the distribution and determinants in the MS population) patients overestimated their two and ten year risk of wheelchair dependency, but underestimated their lifetime risk (Janssens et al., 2003).

One-third of patients perceived the ten year or lifetime risk to be about 50%. A more qualitative exploration was conducted by interviewing patients about their perception of the ten year risk. Results from these interviews indicated that these “50%” responders reported significantly more uncertainty than the remaining two-thirds of patients.

Explanations like ‘I don’t know’ (3.80-fold increase compared with others, $p < 0.001$) and ‘It might happen, or it might not happen’ (30-fold increase compared with others, $p < 0.001$) were used significantly more often by the “50%” responders. Patients who had more functional limitations (as measured by the EDSS) perceived themselves to be at higher risk of wheelchair dependency at each time point. Perceptions of risk were not related to sex, age, diagnostic certainty (definite versus probable MS) or time since diagnosis/first symptoms.

Similar percentages of patients reported that their risk of MS worsening over the next two, five and ten years was likely/extremely likely (18.80%, 34.80% and 52.20%, respectively; Glanz et al., 2016). Patients with a higher EDSS, or a progressive disease course, perceived themselves to be at higher risk of progression at each time interval. Patients with a higher relapse rate over the last year rated the risk of progression at ten years to be more likely, but not at two or five years.

Patients considered wheelchair dependency a serious consequence of their disease at all time points (two years: mean VAS = 82.50, $SD = 19.70$; ten years: mean VAS = 74.50, $SD = 22.90$; lifetime: mean VAS = 71.60, $SD = 24.00$). Patients with more disability perceived wheelchair dependency to be less serious ($p < 0.01$). Perceptions of risk were not related to sex, age, diagnostic certainty (definite versus probable MS), time since first symptom or time since diagnosis.

Janssens et al. (2003) suggested that differences in functional ability alter the need and significance of a wheelchair and its seriousness. Patients with limited walking ability may see a wheelchair as a means to increase their mobility, whereas those who are currently fully mobile, may perceive a wheelchair as a more serious consequence. The findings of this study are limited by its small sample size.

Janssens et al. (2004) investigated the impact of perceived risk of wheelchair dependency on anxiety, depression and disease-related distress. After controlling for EDSS, time since first symptoms, time since diagnosis, age and sex, authors found that patients with higher perception of risk and seriousness of wheelchair dependency were more distressed by intrusions of MS-related thoughts and feelings. This relationship was found for two year, ten year and lifetime risk of wheelchair dependency. Only the two year risk and seriousness of wheelchair dependency was related to anxiety and depression. The results need to be interpreted with caution given that this is the first study to use the IES to assess psychological distress related to the diagnosis of a chronic disease. The reliability and validity of using such measure in this population could be questioned.

In terms of generalisability, patients in Janssens et al. (2003) had all been diagnosed within the two years prior to the study, however the sample investigated by Glanz et al. (2016) were an average of 15.50 years from onset, therefore reflective of a broader, more generalisable sample.

Taken together these findings indicate that patients have high levels of uncertainty regarding risk of wheelchair dependency and raise the question whether the perception of prognostic risks can be improved in the clinical setting.

2.4.2.3. Risk perception in treatment

MS drugs have different and complex risk-benefit profiles (Angelis et al., 2018). The perceived likelihood of benefits and risks related to the medication taken for MS was assessed in four studies using a range of methods including a VAS (Heesen et al., 2010; Heesen et al., 2017), a 5-point scale (Glanz et al., 2016) and multiple-choice questions (Hofmann et al., 2012).

To assess perceived efficacy of Natalizumab, patients were asked to estimate how many patients taking/not taking Natalizumab would be wheelchair dependent within ten years and how many patients would not be able to walk more than 100m. Patients were given eleven multiple-choice answers for both questions, answers were presented as follows: <10, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 of 100 treated patients (Heesen et al., 2010).

General PML risk was assessed using a VAS, with its points anchored at 0=no risk and 10=high risk (Heesen et al., 2010). Similarly, Heesen et al. (2017) used a VAS to ask patients about their perceived general PML risk, ranging from 1=low, to 25=high.

General PML risk was perceived as moderate (mean VAS = 4.5; Heesen et al., 2010; mean VAS = 11; Heesen et al., 2017). Overall, patients overestimated the benefit of Natalizumab (Heesen et al., 2010). A multiple regression model indicated that the perception of general PML risk was higher in women. Patients who had lived with MS for a long time and received Natalizumab for a long time perceived the general risk as lower (Heesen et al., 2017). Given this finding it was suggested that patients may have to some degree adapted to the risks of treatments (Heesen et al., 2017).

Another study used a VAS to assess general risk perception of Mitoxantrone and perception of individual risk for leukaemia (an adverse risk associated with the medication; Hofmann et al., 2012). Points on the VAS were anchored at 0 (low risk) and 10 (high risk). Patients perceived the general risk of Mitoxantrone as significantly higher than the risk patients attributed to themselves (Hofmann et al., 2012). Hoffman et al. (2012) suggest that the results from their study are reflective of people with MS having an optimistic bias in their own personal risk attribution compared to the general risk perception.

Glanz et al. (2016) asked patients to estimate the minor and serious side effects of commonly prescribed MS drugs on a five point scale, ranging from extremely unlikely to extremely likely. Interestingly, when asked to estimate the minor and serious side

effects of commonly prescribed MS drugs, patients' most common response was 'Don't know'. Patients were unwilling to estimate the risk of side effects related to DMDs that they had not been prescribed (Glanz et al., 2016). It was suggested these results may indicate that patients with MS do not have enough knowledge about the side effects of DMDs to enable sufficient decision-making when it comes to the risks and benefits.

The results need to be considered in the context of a possible selection bias: one study did not provide data on reason for exclusion of patients from the final sample (Heesen et al., 2017). The results are limited by the study's moderate response rate and its retrospective design (Hoffman et al., 2012).

In summary, the literature suggests that MS patients report uncertainty regarding the risks associated with DMDs. Patients perceive the general risk to be higher than the risk they attribute to themselves. These results are to be considered in the context of methodological limitations.

2.4.3. Risk attitude

Risk attitude is used to describe an individual's decision-making in terms of taking or avoiding risk, when deciding how to proceed under conditions of uncertainty (Rosen et al., 2003). Risk attitude was measured in three studies (Prosser et al., 2007; Glanz et al., 2016; Bsteh et al., 2017).

One study recruited patients with MS and measured their general risk attitude by using two rating scales in addition to a standard gamble scenario (Glanz et al., 2016).

Participants were first given a single-item of risk orientation that asked patients to rate their overall comfort with taking risks from “extremely comfortable” to “extremely uncomfortable” on a five point scale. Participants were then given a Risk Propensity Scale (RPS), which is a seven-item self-report measure of an individual’s propensity to take general/health and safety risks. Researchers also used a standard gamble scenario which asked participants to consider a new MS drug that would enable patients to be relapse free, with no worsening of symptoms but a possible side effect was death.

Participants rated the likelihood that they would take the new drug, if the risk of death was either 1:2, 1:10, 1:100, 1:1,000, 1:10,000 or 1:100,000.

The majority of participants were risk neutral on the single-measure of risk orientation. In contrast, the mean risk propensity score on the RPS indicated an overall aversion to issues related to health and safety (Glanz et al., 2016). 65% of patients reported that they were risk adverse when it comes to risks associated with their health. This aversion to taking risks related to health was confirmed on the standard gamble scenario: almost 50% of participants reported that they were unlikely/extremely unlikely to take the drug even if the probability of death was 1:100,000. There were no significant associations between risk orientation scores or RPS scores and gender, age, race, marital status, EDSS, disease course or relapse rate. On the gamble scenario, males were significantly more likely to take treatments that carried risk of death at a risk rate of 1:10,000 or 1:100,000, than females. Although advantageous to measure risk in three different

ways, it is unclear how representative the sample is, as patients were recruited from one centre during a five-week period (Glanz et al., 2016).

Another study recruited patients with RRMS and assessed risk attitude using a standard gamble question on health outcomes (See Figure 3). The number of relapse-free days in Box 2 which causes the subject to choose Box 3, was used as a proxy for the patients risk attitude regarding health, authors terms this ‘the certainty equivalent’ (Prosser et al., 2002). For example, if a person were risk neutral, then their response would be fifteen relapse-free days. A risk-averse person would accept Drug B even if the number of relapse-free days was less than fifteen. A risk-seeking person would not accept Drug B unless the number of relapse-free days was more than fifteen. The mean certainty equivalent was 14.6 and the median certainty equivalent was fifteen relapse-free days. Seven patients showed extreme risk-averse behaviour, accepting the lowest offer. Ten patients showed extreme risk-seeking, accepting the highest offer. Results of a multinomial logistic regression revealed that the coefficient for the certainty equivalent on health was significant and positive for patients that had never been on treatment. This finding suggests that when patients are more risk-seeking they are more likely to be in the ‘never-on-treatment group’ compared to the group with ‘excellent adherence’ (Prosser et al., 2002).

Suppose that you are at the beginning of a relapse which will last 30 days. Imagine that we can offer you a choice of two drugs, Drug A and Drug B. Drug A has a 50% chance of immediately ending the relapse and a 50% chance that it will not work at all. Drug B will work for certain, but is less effective. It can reduce the length of a relapse from 30 days to less than 30 days.

Now imagine that you can choose between the following treatment options. Click in the box you prefer.

[Box 1]

Drug A has a 50% chance of ending the relapse immediately, and a 50% chance of not working at all.

[Box 2]

Drug B reduces the relapse from 30 to 29 days.

[Box 3]

It is too hard to choose.

If the subject chooses Box 1 or Box 2, the computer program will then vary the number of days by which Drug B reduces the relapse in Box 2 until the subject chooses Box 3.

Figure 3. Standard gamble scenario on health outcome. Reprinted from “The Relationship between Risk Attitude and Treatment Choice in Patients with Relapsing-Remitting Multiple Sclerosis”, by L. Prosser, K. Kuntz, A. Bar-Or and M. Weinstein, 2002, *Medical Decision Making*, 22(6), p. 508.

Risk attitude was assessed via the Urgency, Premeditation, Perseverance, Sensation Seeking, Positive Urgency (UPPS) Impulsive Behaviour Scale and The Domain-specific risk taking scale and comparing patient scores to published normative controls (Bsteh et al., 2017). Patients did not significantly differ from the respective normative samples for the UPPS Impulsive Behaviour Scale and the Domain-specific risk taking questionnaire. Researchers excluded patients that had severe cognitive problems, which limits generalizability (Bsteh et al., 2017). The conclusions need to be interpreted with

caution given the small sample size, which limits the power of comparisons between samples (Bsteh et al., 2017).

Healthy members of the community (control group) and patients with MS were given gamble scenarios, two based on money outcomes and one based on health outcomes (See Figure 4). Using a control group allows comparison of how MS patients' perceptions compare to the general population. Patients were predominantly risk neutral with respect to health outcomes and risk averse with respect to money outcomes (Prosser et al., 2007). There were no differences between MS patients and healthy controls. The conclusions need to be interpreted with caution given the small sample size (Prosser et al., 2007). The accuracy of the novel method of creating a health metric to measure risk by using methods tested with monetary outcomes could be questioned. It is also important to draw attention to the fact that only one question was asked regarding health, which is a small basis on which to confirm/disconfirm the findings in relation to health.

a. Standard-gamble question on money outcomes: money lottery—small

In this section, you will be asked to consider whether you would prefer different types of "lottery tickets" to a certain outcome.

The next two questions will ask you to choose between a hypothetical lottery ticket and a certain option. For example, the first question will ask you to consider a hypothetical lottery ticket that offers a chance to win \$100.

Lottery ticket 1:

50% chance of winning \$100 and a 50% chance of winning nothing

The question will then ask you, if you had the opportunity to accept some certain amount of money or you could accept the lottery ticket, what is the least amount of money that would make you indifferent between the two choices?

For example:

Would you prefer \$50 to lottery ticket 1? How about \$30? \$20? And so on.

Now imagine that you can choose between the following boxes. Click in the box you prefer.

[Box 1]

Accept \$0.00 for sure.

[Box 2]

Lottery ticket with a 50% chance of winning \$100 and a 50% chance of winning nothing.

[Box 3]

It is too hard to choose.

If the subject chooses box 1 or box 2, the computer program will then vary the number of dollars in box 1 until the subject chooses box 3.

b. Standard-gamble question 2 on money outcomes: money lottery—large

Lottery ticket 2:

50% chance of winning \$15,000 and a 50% chance of winning \$5000

Now imagine that you can choose between the following boxes. Click in the box you prefer.

[Box 1]

Accept \$5000 for sure.

[Box 2]

Lottery ticket with a 50% chance of winning \$15,000 and a 50% chance of winning \$5000.

[Box 3]

It is too hard to choose.

c. Standard-gamble question on health outcomes

Suppose that you are at the beginning of a relapse that will last 30 days. Imagine that we can offer you a choice of two drugs, drug A and drug B. Drug A has a 50% chance of immediately ending the relapse and a 50% chance that it will not work at all. Drug B will work for certain but is less effective. It can reduce the length of a relapse from 30 days to less than 30 days.

Now imagine that you can choose between the following treatment options. Click in the box you prefer.

[Box 1]

Drug A has a 50% chance of ending the relapse immediately and a 50% chance of not working at all.

[Box 2]

Drug B reduces the relapse from 30 to 29 days.

[Box 3]

It is too hard to choose.

If the subject chooses box 1 or box 2, the computer program will then vary the number of days by which drug B reduces the relapse in box 2 until the subject chooses box 3.

Figure 4. Standard gamble scenario on health outcome. Reprinted from “Do Risk Attitudes Differ across Domains and Respondent Types”, by L. Prosser and E. Wittenberg, 2007, *Medical Decision Making*, 27(3), p. 283.

In summary, the findings regarding patients’ risk attitude are mixed. One study found that patients were risk neutral regarding health outcomes and concluded that there was no difference in risk attitude between MS patients and healthy controls (Prosser et al., 2007). However, other research reports that MS patients have an overall risk aversion to issues related to health (Glanz et al., 2016). These discrepancies could be explained by the different methods of assessment. Findings suggest that risk attitude may be related

to treatment choice; the more risk seeking the individual, the more likely they are to choose no treatment (Prosser et al., 2002). It is also important to note the general limitation of asking patients to respond to hypothetical treatment scenarios; hypothetical decisions might be very different to those made in the real world.

It has been suggested that changes in risk attitude in MS patients could be due to a state of ‘transient sickness behaviour’ that is related to an acute relapse rather than persistent changes in attitude (Bsteh et al., 2017). Interestingly, one study which excluded patients with a relapse within 24 weeks prior to assessment found no difference in risk attitude compared to controls (Bsteh et al., 2017).

2.4.4. Risk knowledge

Risk knowledge is necessary to enable patients to make informed choices and it had been found to contribute to treatment adherence (Costello, Kennedy, Scanziollo, 2008). Nine studies measured risk knowledge about prognosis and treatment by using self-report questionnaires (Heesen et al., 2004; Hofmann et al., 2012; Heesen et al., 2017; Kopke et al., 2014; Kopke et al., 2017; Bichuetti et al., 2018; Bruce et al., 2018a; Bruce et al., 2018b; Giordano et al., 2018). Patients were given a 19-item risk knowledge questionnaire and a mean knowledge score was calculated based on the correct answers (Heesen et al., 2004; Kopke et al., 2014). Giordano et al. (2018) used the same measure to investigate risk knowledge but conducted the study in eight countries in order to investigate cross-cultural differences in MS risk knowledge. One study assessed knowledge of the risk of developing PML by five multiple choice answers, ranging

from 1:200 to 1:100,000 and calculating a mean knowledge score (Bichuetti et al., 2018). Heesen et al. (2017) presented patients with seven multiple choice questions about PML risk factors and a mean knowledge score was calculated based on correct answers. Hofmann et al. (2012) assessed risk knowledge via a questionnaire that contained items such as effects and side effects of treatments. Patients completed a 25-item multiple choice questionnaire on general MS knowledge (Bruce et al., 2018a; Bruce et al., 2018b).

The level of overall risk knowledge regarding treatment was low, with only a small percentage of questions answered correctly (Heesen et al., 2004; Kopke et al., 2014; Kopke et al., 2017). Risk knowledge was low in all countries, the mean number of correct answers in the sample was 8.70 out of 21, indicating a mean correct score of 41% (Giordano et al., 2018). Germany and Serbia showed the best results with about 52% correct answers (Giordano et al., 2018).

Patients generally underestimated the risk associated with Mitoxantrone (Hofmann et al., 2012). It has been reported that patients generally understood the risks associated with Natalizumab (Bichuetti et al., 2018). However other findings suggest patients underestimated the hypothetical risk of PML after two years of therapy (Heesen et al., 2017). Variables that were significantly associated with risk knowledge were higher education, previous DMD experience and a correct answer to medical data interpretation question (Giordano et al., 2018). Higher MS knowledge was associated with more willingness to initiate a DMD (Bruce et al., 2018a; Bruce et al., 2018b).

Patients with the highest knowledge scores had been diagnosed within the past two years (Heesen et al., 2004). It was suggested that risk knowledge depends on the actual relevance of the information, which is higher in early stages of MS, when patients are making decision about DMDs, with discussion regarding risk occurring at diagnosis.

The findings need to be interpreted in the light of the 20% non-response rate, which limits the representativeness of the sample (although the authors note that the demographic data of the non-responders did not suggest that they formed a separate subgroup) and its retrospective design (Hofmann et al., 2012). One study recruited patients across six sites, which increases the likelihood that findings will be generalisable. However, the external validity is questionable as recruitment took part through academic centres (Kopke et al., 2014). A more recent study addresses this limitation by recruiting patients through in and outpatient programmes, minimising selection bias (Kopke et al., 2017).

Overall, the findings of these studies suggest that patients with MS have a low level of risk knowledge. Some of the research suggests that this leads to patients underestimating DMDs risks, whereas one study found that patients generally understood the risks. These conclusions need to be interpreted with caution given the methodological flaws.

2.4.5. Risk tolerance and risk acceptance

Risk tolerance and risk acceptance were assessed using either hypothetical scenarios

(Tur et al., 2013; Bruce et al., 2018a; Bruce et al., 2018b; Fox et al., 2019), real DMD information (Heesen et al., 2010; Heesen et al., 2017) or a combination of both (Fox et al., 2015; Bichuetti et al., 2018).

Tur et al. (2013) presented patients with five hypothetical scenarios which had different associated risks of serious side effects. Patients were asked to what extent they would like to continue receiving a drug if the associated annualised risk of a serious side effect was 1/2,000,000 (very low), 1/600,000 (low risk), 1/5,000 (intermediate risk), 1/1000 (high risk) and 1/50 (very high risk). Patients answered using a VAS, with values ranging from 0-10 (0=I would not like to continue receiving this drug at all; 10=I would like to continue receiving this drug without any doubt). The authors created risk-acceptance scores (RAS) for each scenario, where higher RAS indicated better acceptance of risk. They also averaged RAS for the high and very high-risk scenarios to obtain a 'averaged RAS' score which indicated the level of acceptance for high and very high risk associated with treatments. Patients taking Natalizumab showed significantly higher RAS across all five scenarios than patients taking other DMDs, suggesting a higher acceptance of risks associated with treatments. Researchers also found the higher the risk of the scenario, the lower the RAS. When groups were analysed as a whole, there was a trend towards a relationship between higher averaged RAS and higher perceived disease severity.

A recent study assessed individual risk by presenting patients with a hypothetical therapy with a fixed benefit of 50% reduction in clinical relapse rate and 30% reduction in disability progression (Fox et al., 2019). These percentages were chosen as they

reflect the efficacy of the majority of current DMDs. A standard gamble scenario was used to assess the risk tolerance for each of the 6 risks. The risks were 1) risk of infection such as bladder and respiratory, which may occasionally require hospitalisation; 2) thyroid injury, which may require lifelong thyroid medication; 3) skin rash, which may be serious enough to require hospitalisation; 4) liver injury, which may require repeated blood test monitoring; 5) kidney injury, which may require lifelong dialysis; and 6) risk of PML, which could be fatal. The odds for each risk were changed to identify the maximum risk tolerance for each patient. The lowest anchor point was 0 (never take any risk for the benefit) to 1 (will take any risk for the benefit). Fox et al. (2019) found that patients reported highest tolerance for infection or thyroid complications (median risk tolerance = 1:1,000 for both). The next highest tolerance was for skin rash (1:2,000), followed by liver injury (1:10,000). The lowest risk tolerance was for both kidney injury and PML (1:1,000,000).

Risk tolerance results indicated that a large proportion of patients were risk averse. Risk tolerance is also affected by the precise risk being evaluated. Some side effects are more acceptable than others. Across all scenarios, men, younger patients and those with a greater disability reported higher tolerance of risk. Those currently taking MS therapy reported higher tolerance than those not taking therapy. Patients taking infusion therapies reported higher tolerance to all risks and those taking injectables reported lower tolerance.

Bruce et al. (2018a) asked patients to indicate their likelihood (0-100%) of taking a hypothetical DMD in terms of side effect probabilities (11 values from .10% to 99.90%)

and reported medication efficacies (11 values from .10% to 99.90%). Bruce et al. (2018b) tested a probability discounting model to explore the independent influences of risks and benefits when patients make hypothetical treatment decisions. Patients with a primary progressive course reported increased DMD willingness, compared to patients with RRMS and SPMS. Patients were less willing to initiate DMD across a range of efficacies and side effects if they had never taken a DMD (Bruce et al., 2018a). Bruce et al. (2018b) found that high rates of discounting based on risks were associated with poor treatment adherence and less disease specific knowledge. High rates of discounting benefits were associated with poorer cognitive functioning.

Patients were asked to choose the risk level at which they would stop Natalizumab treatment, given different risk probabilities of PML (Heesen et al., 2010; Heesen et al., 2017). 17% of patients indicated they would stop treatment at an adverse event rate of 1:10,000 or lower, 54% of patients would stop at an event rate of 1:100 and 29% would accept higher risks (Heesen et al., 2010). Heesen et al. (2017) reported similar results with 40% of patients indicating that they would accept a PML risk of higher than 100/1000.

Two standard gamble scenarios were used to assess risk tolerance (Fox et al., 2015). One scenario promised a complete and permanent reversal of MS symptoms, but had a risk of painless, immediate death in sleep. The second scenario was taking the real-life treatment Natalizumab, with risks and benefits as documented in previous clinical trials. Starting with a complication risk of 1:1,000 for each scenario, patients were asked if they would accept treatment with each degree of risk for the associated benefit. Fox et

al. (2015) found that three-quarters of people had a tolerance for risks lower than 1:1,000, indicating that they were risk averse and not willing to take high risks for greater benefits. Patients with greater disability tolerated greater risks for a treatment that would either cure or slow disease progression.

Bichuetti et al. (2018) presented patients with the same hypothetical scenarios and same method as previous researchers (Tur et al., 2013), in order to calculate a RAS. In addition patients were asked to stipulate the level of risk they considered high enough to stop or be unwilling to receive Natalizumab. Patients' RAS was lower than that of patients previously interviewed, suggesting a lack of willingness to take risks with hypothetical drugs (Tur et al., 2013; Heesen et al., 2010). The older the patient, the more likely there were to accept higher risks (Bichuetti et al., 2018). The ability to take risks was not associated with years of education, the authors suggested that this reflects that all patients interpreted the questions equally. The fact that years of education was not measured in the earlier study may account for the difference in findings. 76% of patients considered a PML risk of 1:1,000 would stop them using Natalizumab. This is a lower threshold than previously reported (Heesen et al., 2010).

In terms of limitations the sample size of one of the studies is relatively small ($n = 69$), although recruiting from two different outpatient centres ensures that the findings are more representative (Heesen et al., 2010). This finding was replicated in a more recent study by the same authors, using a larger sample (Heesen et al., 2017). Cognition or education was not assessed, therefore it is unclear whether patients fully understood the contents and therefore not factoring in their ability to make decisions.

Furthermore the RAS is not a validated way to assess risk (Tur et al., 2013). Given that the sample of one of the studies was from Brazil, the results may not be generalisable to the whole country or beyond, or relevant to a European context (Bichuetti et al., 2018). It is also important to note that not all of the studies state whether or not the patients are currently taking treatment. This is crucial information, given that it is likely that their current situation will impact on decision-making. Some of the drugs have higher risk profiles than others; it is important that studies stipulate what the current treatments are and ensure that they report any associations.

In summary, the results are mixed in relation to level at which patients are willing to accept risks, these results need to be considered with caution due to the limitations described. Although risk tolerance is variable among patients with MS, a large proportion are risk averse. Risk acceptance seems to be related to age, disease severity, type of MS and current DMD.

Table 5

Outcomes of studies assessing risk

Study (first author, year)	Control group	Cognitive measure	Mood measure	Risk attitude	Risk perception	Risk knowledge	Risk tolerance/risk acceptance	Results
Janssens, 2003	-	-	-	-	Perceived likelihood and seriousness of becoming wheelchair-dependent (2 years, 10 years, lifetime) measured on a VAS. Patients were interviewed about their perception of their 10-year risk.	-	-	Patients overestimated their 2 year and 10 year risks of wheelchair dependency, but underestimated their life time risk. Patients considered themselves to be at higher risk of wheelchair dependency if they had more functional limitations. Wheelchair dependency was rated a serious consequence of MS. Patients with more functional limitations had lower perceptions of seriousness.

Study (first author, year)	Control group	Cognitive measure	Mood measure	Risk attitude	Risk perception	Risk knowledge	Risk tolerance/risk acceptance	Results
Janssens, 2004	-	-	HADS IES	-	Perceived likelihood and seriousness of becoming wheelchair-dependent (2 years, 10 years, lifetime) measured on a VAS.	-	-	<p>Patients with more physical limitations had significantly higher perception of the 2year, 10year and lifetime risk of wheelchair dependence, but considered wheelchair dependence to be less serious.</p> <p>Patients with higher disability reported significantly more symptoms of depression and anxiety. 34% had clinically relevant levels of anxiety and 10% of depression.</p>

Study (first author, year)	Control group	Cognitive measure	Mood measure	Risk attitude	Risk perception	Risk knowledge	Risk tolerance/risk acceptance	Results
Heesen, 2004	-	-	-	-	-	MS risk knowledge questionnaire (19-item).	-	Overall, risk knowledge was low, with only a small percentage of questions answered correctly. Highest scores were seen in patients who had been diagnosed within the past 2 years.
Prosser, 2002	-	-	-	Standard gamble scenario on health outcomes.	-	-	-	More risk seeking, less likely to choose treatment compared with more risk adverse patients ($p<0.01$).
Prosser, 2007	Healthy members of the community.	-	-	Both groups were given standard gamble scenarios, two based on money and one based on health outcomes.	-	-	-	Patients were predominantly risk neutral with respect to health outcomes and risk averse with respect to money. No difference in response of patients and healthy controls.

Study (first author, year)	Control group	Cognitive measure	Mood measure	Risk attitude	Risk perception	Risk knowledge	Risk tolerance/risk acceptance	Results
Heesen, 2010	-	-	-	-	Asked to rate perceived severity of MS as a disease on a VAS (0-10, 10=high malignancy). Asked to estimate how many participants with and without Natalizumab would end up wheelchair dependent in 10years, using a VAS and how many people would not be able to walk more than 100m. Asked to rate general risk of PML.	-	-	<p>Patients perceived MS to be a severe disease.</p> <p>Patients overestimated the effects of Natalizumab.</p> <p>Rated PML risk as moderate.</p>

Study (first author, year)	Control group	Cognitive measure	Mood measure	Risk attitude	Risk perception	Risk knowledge	Risk tolerance/risk acceptance	Results
Hofmann, 2012	-	-	-	-	VAS to assess general mitoxantrone risk perception and individual risk.	Risk knowledge and awareness questionnaire including side effects of treatment and disease course.	-	Patients perceived general risk was significantly higher than the risk patients attributed to themselves.
Tur, 2013	DMD group	-	-	-	Rate perceived severity of MS as a disease on a VAS. Asked to rate in general and in their case.		VAS to rate extent to which they would continue receiving a drug if associated annual risk of serious adverse event was very-very high. Higher RAS indicated a better acceptance for risk.	Underestimation of risks associated with Mitoxantrone. Patients considered their own disease was significantly less severe than was MS in general. The higher the risk the hypothetical scenario had, the lower the RAS. Trend towards higher RAS and higher severity perception. Nat group has higher RAS than control group.

Study (first author, year)	Control group	Cognitive measure	Mood measure	Risk attitude	Risk perception	Risk knowledge	Risk tolerance/risk acceptance	Results
Kopke, 2014	CG=standard information IG=education programme	-	HADS	-	-	Risk knowledge was assessed using a 19-item multiple-choice questionnaire.	-	Baseline mean scores on the HADS were low. Low level of risk knowledge. At baseline, overall risk knowledge was low, with only 32 out of 93 people in the intervention group answering more than 11 of 19 questions correctly and only 22 of 99 people in the CG answering more than 11 of 19 questions correctly.

Study (first author, year)	Control group	Cognitive measure	Mood measure	Risk attitude	Risk perception	Risk knowledge	Risk tolerance/risk acceptance	Results
Fox, 2015	-	-	-	-	-	-	Online standard gamble paradigm for 2 scenarios, one offering a completed cure for MS at the risk of painless death in sleep and the other offering Natalizumab with its associated risks and benefits.	Median risk tolerance for both scenarios was 1:10,000. Over 3% were willing to take any risk for either of scenarios. 15-23% were highly risk averse and would accept no risk. Three-fourths of patients had a risk tolerance lower than 1:1000 for both scenarios. Disability and current treatment with Natalizumab were strongly associated with higher risk tolerance.

Study (first author, year)	Control group	Cognitive measure	Mood measure	Risk attitude	Risk perception	Risk knowledge	Risk tolerance/risk acceptance	Results
Glanz, 2016	-	-	-	<p>Single-item of risk orientation that asks participants to rate their overall comfort with taking risk.</p> <p>Risk Propensity Scale-a 7 item self report measure of individual propensity to take general/health and safety risks</p> <p>Standard gamble scenario</p>	<p>Perceived likelihood of becoming wheelchair-dependent (2 years, 5 years, 10 years) measured on a 5 point scale, ranging from extremely likely to extremely unlikely.</p> <p>Estimated the likelihood of minor and serious side effects of DMDs.</p>	-	-	<p>18.80% of patients reported their risk of MS worsening over in 2 years as likely/extremely likely, 34.80% in 5 years and 52.20% in 10 years. Those with higher disability perceived themselves to be at higher risk of progression at 2, 5 and 10 years.</p> <p>Uncertainty regarding side-effects associated with DMDs.</p> <p>Participants were risk neutral on the single measure of risk orientation and risk averse on issues related to health and safety.</p>

Study (first author, year)	Control group	Cognitive measure	Mood measure	Risk attitude	Risk perception	Risk knowledge	Risk tolerance/risk acceptance	Results
Bichueti, 2018	-	-	-	-	Rate perceived severity of MS as a disease on a VAS (0=not at all, 10=most severe thing I can think of).	Mean knowledge score based on correct answers to a multiple choice questionnaire about risk.	-	<p>Patients perceived MS to be a severe disease.</p> <p>Patients understood the risks associated with Natalizumab. Patients considered the risk of PML as moderate to high.</p>
Bsteh, 2017	Compared scores to published norms.	-	BDI-II	Patients were given the UPPS impulsive behaviour scale and The domain specific risk taking scale.	-	-	-	<p>Four patients had a score of ≥ 18 indicating depression. These patients did not differ from patients without depression in terms of risk behaviour.</p> <p>No significant alterations of risk attitude in MS patients compared to healthy controls.</p>

Study (first author, year)	Control group	Cognitive measure	Mood measure	Risk attitude	Risk perception	Risk knowledge	Risk tolerance/risk acceptance	Results
Heesen, 2017	-	SDMT	-	-	<p>Rate perceived severity of MS as a disease on a VAS (1=benign, 25=severe).</p> <p>Rate seriousness of becoming wheelchair dependent.</p> <p>Patients were asked for their assessment of PML risk in general on a VAS (1=low, 25=high) and their perceived personal risk.</p>	<p>7 multiple choice questions on PML risk factors were presented.</p> <p>Mean knowledge score calculated.</p>	-	<p>35% of patients were considered to have a cognitive deficit.</p> <p>Patients perceived MS to be a severe disease. Men perceived MS as more severe than women and perception of severity increased with age as well with increased disability.</p> <p>Becoming wheelchair bound was rated as a serious complication.</p> <p>General PML risk rated as moderate.</p>

Study (first author, year)	Control group	Cognitive measure	Mood measure	Risk attitude	Risk perception	Risk knowledge	Risk tolerance/risk acceptance	Results
Kopke, 2017	CG=standard information IG=education programme	-	HADS	-	-	Risk knowledge assessed by using a risk knowledge questionnaire. A cut-off of 9 or more correct answers was defined as adequate risk knowledge.	-	14% of intervention group and 16% of control group had adequate risk knowledge at baseline. Indicating a low level of risk knowledge. No baseline HADS score were reported.
Bruce, 2018a	-	-	-	-	-	Medical decision-making task patients indicated their likelihood (0-100%) of taking a hypothetical DMD as the probability of mild side effects varied.	-	Patients with a primary progressive course reported increased DMD willingness compared to patients with relapsing-remitting and secondary-progressive courses. Patients were less willing to initiate DMD if they had never taken a DMD.

Study (first author, year)	Control group	Cognitive measure	Mood measure	Risk attitude	Risk perception	Risk knowledge	Risk tolerance/risk acceptance	Results
Bruce, 2018b	-	Cognitive composite score using Symbol Digit Modalities Test, The Rey Auditory Learning Test, Trails B	HADS	-	-	Medical decision-making task (MDMT)-patients indicated their likelihood (0-100%) of taking a hypothetical DMD as the probability of mild side effects and medication efficacies varied. MS knowledge questionnaire-25 multiple choice questions	-	High rates of discounting based on risks were associated with poor treatment adherence and less-disease specific knowledge. High rates of discounting benefits was associated with poorer cognitive functioning.

Study (first author, year)	Control group	Cognitive measure	Mood measure	Risk attitude	Risk perception	Risk knowledge	Risk tolerance/risk acceptance	Results
Giordano, 2018	-	-	-		-	Risk knowledge questionnaire (RIKNO) Self-assessed inventory consisting of 19 multiple-choice items; a total score (0-21) obtained by summing correct answers.	-	Mean number of correct answers on RIKNO was 8.70 (SD= 3.50) out of 21, indicating that participants got an average of 41% of answers correct. Indicating that overall risk knowledge was low. Variables significantly associated with RIKNO were country, previous DMD experience. Education and fear of wheelchair dependency.

Study (first author, year)	Control group	Cognitive measure	Mood measure	Risk attitude	Risk perception	Risk knowledge	Risk tolerance/risk acceptance	Results
Fox, 2019	-	-	-	-	-	-	Risk preference and acceptance was measured by describing a hypothetical treatment with varied complications.	Participants exhibited highest tolerance for injection and thyroid injury (1:1,000) and the least tolerance for kidney injury and PML (1:1,000,000). A large proportion were risk averse. 17-39% were unwilling to assume any risk for beneficial therapy. Men were more tolerant to risks than women. Increasing age was associated with lower risk tolerance.

2.5. Discussion and conclusion

2.5.1. Discussion

The present systematic review explored MS patients' risk perception, risk attitude, risk knowledge and risk acceptance/tolerance. Studies included patients with different clinical subtypes of MS. Risk was generally addressed using hypothetical scenarios with differing risk and benefits, as part of a larger study. Most of the studies had methodological issues that make it difficult to draw any firm conclusions. These issues are reflected in the scores on the quality assessment tool.

People with MS are faced with the difficult decision of weighing up the complex risk-benefit profiles of DMDs. When in such situations, a shared-decision making approach is deemed as the gold standard. For this to work effectively, it requires understanding of the patients' risk perception, risk attitude, risk knowledge and level of risk that they consider acceptable. It might be possible to assess patients on a variety of risk variables and tailor the approach to support and accommodate their particular risk profile. If this was feasible and then implemented in practice, it could support treatment adherence.

The results will be considered in relation to the research questions. Whilst MS patients perceived MS to be a severe disease (Heesen et al., 2010; Tur et al., 2013; Heesen et al., 2017; Bichuetti et al., 2018), they perceived their own disease as being less severe compared to the general population of people with MS (Tur et al., 2013).

Patients overestimated their two and ten year risk of wheelchair dependency, but underestimated their lifetime risk (Janssens et al., 2003; Glanz et al., 2016). Qualitatively, patients expressed uncertainty regarding their ten year risk. Higher perception of risk and seriousness of wheelchair dependency was related to distress and the short-term risk was related to anxiety and depression (Janssens et al., 2004). It is important that patients understand wheelchair dependency risks, particularly as they were related to anxiety and depression.

Regarding the perception of risk associated with treatments, patients tended to overestimate the benefits of Natalizumab (Heesen et al., 2010). Perception of risk was associated with gender, time since diagnosis and current treatment. Patients perceived the general risk of treatment as significantly higher than the risk that they attributed to themselves (Hofmann et al., 2012). The overestimation of benefits may lead to problems with adherence as people may stop taking drug when they realise that the benefits are not as much as they originally thought they were.

The results regarding risk attitude are mixed, people with MS were risk neutral on a single measure of risk orientation but demonstrated an overall aversion to issues related to health and safety (Glanz et al., 2016). Another study found that patients were risk neutral with respect to health outcomes and risk averse with respect to money outcomes (Prosser et al., 2007). However, it must be noted that researchers are drawing this conclusion from one question related to health. The more risk-seeking patients were, they more likely they were to choose no treatment (Prosser et al., 2002). People with

MS did not differ from controls in terms of risk attitude, which could be explained by limitations with study design (Prosser et al., 2007; Bsteh et al., 2017). Given the finding that risk attitude was related to treatment choice, it is important to take this into account in practice.

Overall, patients' risk knowledge was not accurate and it was judged by authors to be low (Heesen et al., 2004; Kopke et al., 2014; Kopke et al., 2017); this finding was present across a range of countries (Giordano et al., 2018). If patients do not have sufficient risk knowledge, they are not able to usefully participate in the decision making process. The low levels of risk knowledge are concerning, given the finding that more risk knowledge is associated with willingness to take a DMD (Bruce et al., 2018a). Providing patients with information in order to increase their risk knowledge could lead to a greater number of patients on or adherent to, DMDs.

Risk tolerance differs according to sex, age, disability level and current DMD (Tur et al., 2013; Fox et al., 2015; Bichuetti et al., 2018; Bruce et al., 2018a; Fox et al., 2019). A large proportion of MS patients were risk averse (Fox et al., 2015). Risk tolerance is affected by the precise risk being evaluated, with some side effects considered more acceptable than others (Fox et al., 2019). This highlights the importance of taking into account the risks that people with MS consider acceptable, this could result in greater satisfaction with treatment choice and therefore impact on adherence.

In terms of cognition, one study reported no association between cognition and risk measures (Heesen et al., 2017). Patient uncertainty in relation to taking DMDs was

associated with poorer cognitive functioning in the second study (Bruce et al., 2018b). A recent systematic review found that cognitive dysfunction, particularly processing speed and attention had a negative impact on decision-making (Neuhaus, Calabrese, & Annon, 2018). It is therefore crucial that future studies take into account the influence of cognition on decision-making. It is important that cognitive functioning is considered in the shared-decision making process. Patients with poorer cognition may need additional support when evaluating the risks and benefits of DMDs.

Whilst five studies included a measure of mood, only three studies reported results in relation to the mood and risk measures. Depressed patients did not differ significantly from patients without depression in terms of risk behaviour (Bsteh et al., 2017). Mood was not associated with how patients discount treatments based on side-effects (Bruce et al., 2018b). Despite the lack of associations between mood and risk measures, it would be useful for future studies to include a mood measure and report on the association with risk. Given that this would be useful information to have in order to tailor information according during the shared decision-making process.

Bruce et al. (2018b) extend the traditional HBM but proposing that there are individual differences in how patients weigh up treatment risks and benefits. Most patients fall in the middle, but some are willing to take even small risk for larger possible benefits. Patients who often discounted treatments based on the increased probability of side effects also had less MS disease knowledge and worse adherence for treatment.

It is important to note that few studies compared patients with MS to healthy controls.

However, the comparison is complex because people with MS have current drug therapy and experience of personal decisions. It would have been interesting to see the difference in performance between these two groups, given that no one is always entirely correct. Also, there are few longitudinal studies, it would be beneficial to assess patient risk perception at different stages. Rather than a snap shot of risk, longitudinal studies would be more reflective of risk profile over time. It is likely that when trying a second drug people are willing to accept more risk as the first one did not work (Fox et al., 2019).

Overall, differences in patient characteristics and methodology limit the conclusions from such findings. Many of the studies have small sample sizes, low response rates and possible selection bias. The studies are largely one centre, recruiting people with MS who are in contact with health services. In general, it is hard to make comparisons between the studies given the different ways that risk was measured. The validity and reliability of assessing risk with self-report and hypothetical scenarios needs to be considered. Furthermore, researchers claim they are measuring different elements of risk but there is a lot of overlap between the different terms, which makes it difficult to categorise the studies effectively. The limitations of using the EPHPP as a tool to assess the quality of the studies must be considered. The 'overall quality rating' does not provide an accurate indication of the overall quality, since two or more 'weak' rating define a study as being 'weak'. It is important that future studies include cognitive measure and measure of mood, as they are factors that can influence patients risk tendencies.

2.5.2. Practice implications

The practical implications of this review include the need to consider patients' risk perception, risk attitude, risk knowledge and risk acceptance/tolerance in order to facilitate the shared decision-making process. This is particularly important given that elements of risk may impact on the long-term adherence to DMDs. It could be suggested that there is a need for a international consensus project on a perceived risk assessment document, tailored for MS clinics, to inform and optimise education and shared decision-making for various risk profiles.

2.5.3. Conclusion

The present review was the first to our knowledge to bring together evidence about the risk perception, risk attitude, risk knowledge and risk tolerance/acceptance of people with MS. Patients tend to overestimate short-term risks of the disease and underestimate the long-term risks. They also have a tendency to perceive their likelihood or severity of disease related risks as less likely than those for the general population of people with MS. Risk attitude was related to treatment choice. A limitation of the current systematic review is the difficulty with which robust conclusions can be drawn given the variety of methods used to assess risk. It could be suggested that a more consistent way of defining and measuring the different elements of risk in MS is required. There was also variation between the studies in terms of study design and patient characteristics. This limits the ability to draw conclusions and suggests a lack of uniformity across studies that address risk in MS.

3. Empirical Study

The effect of risk propensity on treatment understanding and decisions in MS patients

3.1. Abstract

Multiple Sclerosis (MS) is a chronic inflammatory disorder of the central nervous system. Disease-modifying drugs (DMDs) can significantly reduce relapse rates and disease progression. People with MS face a difficult decision when weighing up the costs and benefits of DMDs. Additional support may be required because people with MS have been shown to make different decisions in the context of risk. This study aimed to confirm whether the Benefit and Risk Information for Medication in Multiple Sclerosis protocol (BRIMMS), is superior to standard presentation in improving patients' understanding of treatments and increasing patient certainty in decisions. The study investigated how self-reported and objective risk attitude, risk perception and propensity to take risks relate to patient understanding scores and certainty in treatment decision. 26 participants were recruited (19 females; 73 %), with a mean age of 42.9 (SD = 10.2). Participants were provided with hypothetical treatment information via the BRIMMS and standard consultation. Understanding of treatment risks and benefits was assessed. The Decisional Conflict Scale was used to assess patients' decisional conflicts regarding their treatment options. Risk was assessed using a single-item measure of risk orientation, the Risk Propensity Scale, a standard gambling scenario and the Iowa

Gambling Task. Cognition, premorbid IQ, mood and fatigue were also assessed. BRIMMS significantly improved patient understanding of treatment risks and benefits and reduced decisional conflict, compared to standard consultation. However, differences in understanding scores were explained by fatigue and depression. There were no associations between self-reported risk attitude, perception or propensity to take risks, understanding or decisional conflict. It is recommended that the BRIMMS should be further evaluated and implemented during consultation in a clinical setting.

3.2. Introduction

Multiple Sclerosis (MS) is a chronic inflammatory disorder of the central nervous system, which often results in neurological disability (Thompson, Baranzini, Geurts, Hemer, & Ciccarelli, 2018). The condition includes sensation, mobility, balance, sphincter, vision and cognition symptoms (Brownlee, Hardy, Fazekas, & Miller 2017). MS can be classified into three main subtypes: Relapsing Remitting MS (RRMS), Secondary Progressive MS (SPMS) and Primary Progressive MS (PPMS). Most people with MS initially experience RRMS, which is characterised by distinct attacks of symptoms followed by either partial or complete remission, which may last months or years (Filippi et al., 2018). Eventually, patients enter the secondary progressive phase, when permanent disability accumulates (SPMS). More rarely, disability accrues from the start (PPMS).

Although there is no cure for MS, disease-modifying drugs (DMDs) can significantly reduce relapse rates and disease progression (Fogarty, Schmitz, Tubridy, Walsh, &

Barry, 2016). However, DMDs are only effective in the relapsing forms of MS, with the exception of Ocrelizumab (licenced for PPMS) and Siponimod (licenced for SPMS).

People with MS face a difficult decision when it comes to weighing up the various costs and benefits of DMDs as the complex risk-benefit profiles are not always correctly interpreted and understood by people with MS (Reen, Silber, & Langdon, 2017a).

Decision-making in these situations may be compromised by the fact that people with MS choose differently when making decisions under risk conditions (Farez, Crivelli, Leiguarda, & Correale, 2014). Furthermore, there is often a difference between patients and health professionals in terms of risk acceptance and risk perception (Heesen et al., 2010).

It is important that patients are able to understand the complex risk and benefit information surrounding DMDs, to inform their decisions about treatment. Shared decision-making as part of a patient-centred approach has been advocated (Barry & Edgman-Levitan, 2012); patient understanding is a prerequisite for successful medical decision-making. Of particular importance is the evidence that shared-decision making is associated with better DMD adherence rates in MS; this is critical as the efficacy of DMDs depends on high levels of adherence (Ben-Zacharia et al., 2018).

The Decisional Conflict Scale (DCS) is a commonly used self-report measure to assess personal values (O'Connor, 1995). The scale assesses patient uncertainty in decision-making and asks questions related to how informed, supported and clear people feel about the decision they are making. Patients report improved satisfaction and less

uncertainty about the course of action to take when partaking in shared decision-making (Shay & Lafata, 2015).

Identifying how to design effective communication of the evidence, regarding the benefits, risks and uncertainty of treatments, in a way that is clear, accessible and usable is a key priority for research. This is highlighted by various government notes (“*PN 500*”, 2017), reports (*The Academy of Medical Sciences*, 2017) and international initiatives (Rieckmann et al., 2018). A recent qualitative study highlights the importance of taking into account the contextual factors (clinical, social and psychological) of patients’ everyday lives when making decisions regarding initiating DMDs (Eskyte et al., 2019).

3.2.1. MS symptoms

People with MS experience a range of symptoms including fatigue, anxiety, depression and cognitive impairments (Thompson et al., 2018). Cognitive deficits, demonstrated at all stages of the disease, are likely to impact on patients’ general understanding and ability to recall important information, which could pose a challenge when deciding on a course of treatment (Reen, Silber, & Langdon, 2017a).

3.2.2. Treatment in MS

People with MS are required to make important decisions about DMDs. These drugs can help with the delay of disease progression, but they are associated with complex

risk-benefit profiles. The DMDs available for the treatment of RRMS vary in efficacy, mode of delivery and adverse event profile (De Angelis, John, & Brownlee, 2018). The breadth of treatments poses challenges in selecting the right treatment for the right patient at the right time (Thompson et al., 2018).

Recent research has explored the differences in the way that health care professionals (HCPs) and people with MS see their needs (Rieckmann et al., 2018). Of particular relevance is the topic of burden of treatment in MS, in which three main areas were identified: risk versus benefit of MS therapies; treatment decisions; and compliance, adherence and monitoring. The review highlighted that there is often a difference between patients and HCPs in terms of risk tolerance. Specifically, people with MS thought that HCPs focus on negative rather than positive aspects of treatment. HCPs reported that they were concerned about the high level of risk patients are willing to take in relation to treatment benefits. The authors stressed the need for the development of patient-centred educational resources that can be used during consultations to enhance disease understanding and improve communication between patients and HCP.

3.2.3. Interventions to support understanding

15 interventions designed to improve MS patients' understanding of the complex risk-benefit profiles of DMDs were reviewed (Reen, Silber, & Langdon, 2017c). Overall understanding of treatment information and risks generally improved after interventions. Improvements in understanding the benefits of treatments were less clear; patients tended to overestimate treatment benefits. Other factors likely to influence

patient understanding of DMDs were not fully investigated in the interventions included in the review. For example, only one intervention examined cognitive impairment.

There was no definitive effect of interventions on DMD decision-making and no one intervention was raised as particularly effective. This review highlighted the need for a standardised evidence-based tool to communicate the risk and benefits of treatments in a way that improves their understanding, whilst taking into account all patient abilities, such as cognitive impairment. Furthermore, a recent review reports uncertainty in relation to the effectiveness of interventions for increasing the use of shared decision-making due to a lack of evidence in the area (Legare et al., 2018).

In light of this, researchers conducted a series of experiments in order to investigate the optimal methods of communicating treatment information to patients with MS (Reen et al., 2018). It was found that MS patients presented with treatment information in frequencies better understood information compared to information presented in percentages or verbal descriptions. They also found that presenting information in bar charts or line graphs was able to improve MS patients' understanding in comparison to pictograms or pie charts. Based on the results of these studies, the authors developed a protocol; the Benefit and Risk Information for Medication in Multiple Sclerosis (BRIMMS), in order to improve patients' understanding and certainty about treatment (Reen et al., 2017b).

The researchers aimed to evaluate the effect of BRIMMS on patients' understanding and confidence in treatment decisions, compared to standard presentation of treatment information used in the UK. A randomised controlled trial was conducted with 24

patients who had a diagnosis of RRMS. Patients were presented with a hypothetical disease (with similar progressive characteristics to MS) and two hypothetical treatments for this disease. The treatment risk-benefit profiles were based on DMD clinical trials in order to be reflective of real life clinical decisions. Risk benefits were presented for one, two and five years of taking the treatment. Each treatment had one minor risk, one adverse risk and one benefit. All patients experienced the four methods of presentation in a random order: BRIMMS protocol (spoken, spoken-written) and standard presentation (spoken, spoken-written). Understanding and decisional confidence were recorded after each condition. Fatigue, depression and anxiety, numerical reasoning, pre-morbid IQ and cognitive abilities were also assessed.

Treatment understanding was significantly affected by conditions: BRIMMS spoken-written produced the best understanding overall. Confidence in treatment decisions was also significantly affected by conditions. Decisional confidence was greater for BRIMMS spoken-written compared to standard. Cognitive factors, pre-morbid IQ, anxiety and fatigue were not related to understanding in the BRIMMS, but had negative influences for standard presentation. Depression did influence understanding on the BRIMMS. This study demonstrated that the BRIMMS protocol offered an effective, evidence-based format for presenting MS medication information. The preliminary experiments looking at different types of format presentations, found that neuropsychological status did influence understanding scores (Reen, Silber, & Langdon, 2018). In the randomised control trial, by chance, there was little neuropsychological impairment within the sample which may account for the lack of association between neuropsychological scores and understanding scores. Consequently, there is a need for

this to be repeated.

3.2.4. MS and risk attitude, perception and propensity

An individual's risk attitude, risk perception and propensity are important factors that may influence the treatment decision-making process. Once the effect of risk attitude, perception and propensity on treatment understanding and decision certainty is known, characteristics of the patients could be determined in advance of the consultation during which the information is presented. The information could be amended to support the shared decision-making process. A recent systematic review looking at methods to investigate patient preferences for treatment identified the influence of risk perception and uncertainty on treatment decisions as neglected research topics (Webb et al., 2018).

Risk attitude is a construct that describes an individual's decision-making in terms of taking or avoiding risk when deciding how to proceed under conditions of uncertainty (Rosen, Tsai, & Downs, 2003). Risk attitude has primarily been studied by using gamble scenarios (Prosser, Kuntz, Bar-Or, & Weinstein, 2002). Authors state that individuals are said to be risk averse if they prefer a lower guaranteed outcome rather than the average value of a gamble. Risk seekers are those that prefer a gamble rather than a guaranteed outcome, with the same average value. Individuals are described as risk neutral if they are indifferent to a guaranteed outcome and a gamble with the same expected value (Prosser et al., 2002).

Risk-taking behaviour may be influenced by more than risk attitude, it may also be the

result of an individual's risk perception, which is the perceived likelihood of experiencing a negative event (Harrison, Young, Butow, Salkeld, & Solomon, 2005). Furthermore, existing research suggests that disease risk perceptions are critical in determining health behaviour (Ferrer & Klein, 2015). Decision-making may also be influenced by an individual's risk propensity, which is defined as an individual's current tendency to take or avoid risk, described as a trait that can change over time as a result of experience (Sitkin & Weingart, 1995). It is therefore likely that decision-making regarding treatments may reflect individual perception of risk, attitude towards risk and risk propensity (Glanz et al., 2016).

Previous research has investigated risk attitude and risk perception in individuals with MS using risk attitude and risk perception rating scales and a standard gamble scenario (Glanz et al., 2016). Interestingly, MS patients were found to be risk neutral overall, but risk averse when issues were related to health and safety. Risk attitude has been found to be related to treatment choice in MS patients (Prosser et al., 2002). Specifically, the more risk-seeking a patient was, the more likely they were to choose 'no treatment' as an option compared to more risk averse patients. Subsequent researchers were interested in assessing the impact of MS on evaluating decision-making under explicit risk (Simioni et al., 2012). Compared to healthy controls, MS patients showed deficits on a task which probed the anticipated effects of decisions outcomes on future choices and MS patients had a greater risk aversion. Patients also differed from controls in the quality of their decision-making. This study highlighted that the quality of decision-making under risk was modified by MS.

Furthermore, results from a recent systematic review looking at decision-making in MS, reported an overall alteration of decision making ability in MS patients compared to controls. Specifically, MS patients' decision-making under risk was altered in 67% of tests analysed and decision-making under ambiguity was affected in 64% of measurements as measured by the Iowa Gambling Task (Neuhaus, Calabrese, & Annon, 2018).

3.2.5. The current study

Further research is needed to confirm whether BRIMMS is superior to presenting information in a standard form (Reen et al., 2017b). The current study will examine whether anxiety, depression, fatigue and cognitive impairment relate to patients' understanding scores on treatments and certainty in treatment decisions. It will also investigate whether BRIMMS is superior to standard presentation in improving patients' understanding scores on treatment and increasing patient certainty in decisions. The current study aims to expand on previous research by investigating how self-reported and objective risk attitude, risk perception and propensity to take risks relate to patient understanding scores and certainty in treatment decision. The research is justified given the lack of studies in this area and the fact that this information could be used to determine patient characteristics in advance of the consultation during which the information is to be presented. It would mean that the presentation of the information could be amended to support the shared decision making process between patient and healthcare professionals.

The current research will be conducted with patients who have RRMS. Patients will then receive hypothetical medication information via both the BRIMMS and standard presentation. In order to assess understanding, patients will be asked questions about the information they received and asked to choose between the two medications they were given. They will also be asked questions in relation to their confidence in that decision. Each patient will be given questionnaires and tasks in relation to mood, fatigue, memory as well as risk attitude, perception and propensity.

3.2.6. Summary

The literature supports the view that patient-centred educational resources can aid in the understanding and certainty of patients' decisions regarding treatment. To understand this further, it is important to replicate previous findings (Reen et al., 2017b). The literature suggests that an individuals' risk attitude, perception and propensity are likely to have an impact on decision-making. There are currently no studies investigating the effect of risk attitude, perception and propensity on decision-making whilst using an educational resource. Therefore, the proposed study would be the first study to investigate the relationship of risk attitude, perception and propensity to decision-making whilst using a standardised protocol. This has clinical implications regarding management, understanding and treatment of individuals with MS.

3.2.7. Research question and hypothesis

3.2.7.1. Confirmatory

Does the BRIMMS improve patients' understanding around treatment risks and benefits compared to standard consultation?

Does the BRIMMS reduce patients' conflict in their treatment decisions compared to standard consultation?

3.2.7.2. Novel

Is self-reported risk attitude, risk perception and propensity to take risks associated with patient understanding and certainty in treatment decisions?

The hypotheses for this study were as follows:

- 1) The BRIMMS protocol would improve patients' understanding of treatment risks and benefits compared to standard consultation.
- 2) The BRIMMS protocol would reduce patients' conflict regarding treatment decisions compared to standard consultation.
- 3) The BRIMMS would be rated more positively by patients than the standard consultation.
- 4) Self-reported risk attitude (Glanz et al., 2016), perception (Glanz et al., 2016) and propensity to take risks (Bechara, Damasio, Damasio, & Anderson, 1994) will predict patient understanding.
- 5) Self-reported risk attitude (Glanz et al., 2016), perception (Glanz et al., 2016) and propensity to take risks (Bechara et al., 1994) will predict patient certainty in treatment decisions.

3.3.Methodology

3.3.1. Research Approval

Following Proportionate Review, a favourable ethical opinion was received from the NHS Health Research Authority (See Appendix A & B). Permission for recruitment of MS participants was given by the Research and Development department at The Royal Free London (Royal Free NHS Foundation Trust; See Appendix C). The experiment also received ethical approval from the Psychology Department Ethics Committee at Royal Holloway, University of London.

3.3.2. Design

The study had a repeated-measures design comparing two formats of presentation of material. A neuropsychological test battery and questionnaire battery were administered to participants.

3.3.3. Participants

A total of 26 patients diagnosed RRMS were recruited. Patients were recruited from The Royal Free London Hospital, NHS Foundation Trust.

3.3.3.1. Inclusion/Exclusion Criteria

Inclusion

All participants:

- were fluent in English.
- were aged between 18 and 65 years.
- had a diagnosis of RRMS by a Consultant Neurologist based on Thompson et al., (2018) criteria.
- were able to give informed consent.
- were able to meet the task demands of the experiment in terms of sensorimotor abilities.

Exclusion

Participants who had:

- significant changes in medication or condition within the last four weeks.
- a history of significant psychiatric disorders, substance or alcohol abuse.
- a significant medical condition (other than MS), personal or social circumstances that were likely to impact on participating in the study.
- significant visual, motor or hearing impairments that would have an impact on their engagement with the tests/protocol/questionnaires.

3.3.4. Recruitment

3.3.4.1. MS Participants Identification

MS participants were recruited from The Royal Free NHS Foundation Trust.

Participants were initially approached by the clinical teams and given a patient

information sheet (See Appendix D). Patients then contacted the researcher to express interest. Alternatively the researcher was present on clinic days and met with patients after they had seen the clinic team (if they had given permission for the researcher to approach them). A leaflet was also created for the purpose of recruitment (See Appendix E). Once contact had been made, a home visit was arranged to gain written consent (See Appendix F) and collect data. All participants were well known to the treatment team and home visits were therefore deemed an appropriate way to collect data. Participants were informed that they were free to withdraw at any time, without giving a reason and informed that this would not impact on their care. This information was provided on the patient information sheet and on the consent form.

3.3.5. Lone Working

The Royal Free NHS Trust Foundation Trust Lone Working Policy (August 2017) was adhered to with risk being assessed on a participant by participant basis and a buddy scheme was in place with the Research Nurse.

3.3.6. Data Storage

Participants were allocated an anonymised participant identification number. Study documentation was kept in a locked cabinet, in a locked room. Data was stored in an encrypted spread sheet.

3.3.7. Power Analysis

A power analysis was conducted using data from Reen et al. (2017b), due to the similarity of the design. The effect sizes range from 0.4 to 0.8 on the validated DCS (O'Connor, 1993). Although the previous study found large effects on the DCS measure when comparing BRIMMS with standard consultations, a conservative medium effect size (0.5) on the DCS will be presumed for this study. It was estimated that for an alpha of 0.05 and power of 0.90, at least 46 MS patients would be required in accordance with procedures (Senn, 1999).

3.3.8. Materials and Methods

Two types of consultation were evaluated in the experiment: standard and BRIMMS. Patients received both conditions. To control for order effects on the BRIMMS and standard consultation, the conditions were counterbalanced; patients were assigned to one of four different orders of presentation (See Appendix G). Half of participants received the BRIMMS first, and half of participants received the standard first. The order of the two hypothetical treatments within each condition was also counterbalanced. The first participant received order one, the second participant received order two, the third participant received order three and so on. The cycle was then repeated, so that the fifth participant received order one, the sixth participant received order two and so on.

Throughout the experiment, patients were given information about one hypothetical disease. Hypothetical information was used in order to avoid discussions surrounding medical information without appropriate professional support. The disease was described as progressive and a list of symptoms were presented (See Appendix H). Patients were told that the hypothetical disease was progressive in nature and could vary between patients, in order to mimic the uncertain and progressive nature of MS. Patients were also told that they might not experience all of the symptoms of the hypothetical disease.

Information was given to participants about two hypothetical treatments, this consisted of one benefit, two minor risks and one adverse risk for each treatment. All information was provided for outcomes associated with short-term (one and two-years) and long-term (five years). All risks and benefits mimicked real-life DMD risk and benefit profiles as closely as possible. The disease and treatment names were those used in the previous experiment (Reen et al., 2017b).

3.3.8.1. BRIMMS

The experimental intervention given to patients was the BRIMMS protocol, which was developed by a previous researcher as a method to present treatment information (Reen et al., 2017b). Participants were provided with a hypothetical clinical trial scenario where the treatment benefits were stipulated for the intervention group (those taking the treatment) and a placebo group (those not taking any treatment).

The BRIMMS was created by considering the results from various experiments, outlined as followed (Reen et al., 2018). All quantitative information was presented using frequencies. Frequencies were presented using the format, N-in-N*X ratio, in which the denominator was kept constant and the numerator was changed to represent the benefit or risk. In addition, information was presented using horizontal bar charts with numbers. Absolute terms were used when presenting the differences in treatment benefits between the intervention group and the control group.

The BRIMMS protocol was provided to patients both verbally and written (See Appendix I). The decision to present BRIMMS simultaneously in both verbal and written form was based on findings from previous experiments which found that BRIMMS spoken-written produced the best understanding overall (Reen et al., 2017b).

3.3.8.2. Standard consultation

The patients received treatment risks and benefits in a standard consultation format as a control condition. The standard consultation was that used in previous work, which had been developed by speaking to MS nurses about how treatment risk and benefit information is presented to patients in consultations (Reen et al., 2017b). The standard consultation was presented to patients simultaneously in both aural and written form (See Appendix J).

3.3.8.3. Outcome measures and assessments to measure patient characteristics

Patient understanding

Understanding of treatment risks and benefits was assessed by asking 15 comprehension questions regarding the side-effects, adverse risks and benefits of each hypothetical treatment (Appendix K). The comprehension questions measured objective knowledge of treatment risks and benefits. The questions were those previously developed by a previous researcher (Reen et al., 2017b; Hamstra et al., 2014; Hawley et al., 2008). Patients could score a maximum of 15 points for each treatment, as 15 questions were asked for each treatment (6 questions for treatment benefits after one year, two-years and five-years, three questions each for the two minor risks after one year, two-years and five-years). Therefore, a total score of 30 was possible for each condition as there were two treatments per condition.

Perceived understanding was assessed as part of three feedback questions measured on a 10-point likert scale, that were asked at the end of each condition. A score of 0=negative rating and a score of 10=positive rating. The questions were ‘How well did you understand the treatment information given to you during this session?’, ‘How satisfied were you with the way treatment information was given to you during this session?’ and ‘How much did you prefer the treatment information given to you during this session?’.

Decisional conflict

The Decisional Conflict Scale (O'Connor, 1995; See Appendix L) is a self-reported questionnaire that was used to assess patients' decisional conflicts regarding their treatment options. After being presented with each set of treatments, patients were required to make a decision regarding treatment (i.e. choose of the two hypothetical treatments, choose neither or say that they were unsure). The option of not choosing a treatment is not present in the original DCS but this was added in order to mimic real clinical decisions in MS (Reen et al., 2017b).

The DCS was given twice to each patient, once after the BRIMMS and once after the standard consultation. After patients made a treatment choice, they were asked to respond to the 16 questions, with three subscales measuring decisional uncertainty and cognitive and social variables thought to be important in the decision making process. A five-point Likert scale (ranging from 0=strongly agree to 4=strongly disagree) is used to score each item. Scores can be standardised to range from no decisional conflict (0) to extremely high decisional conflict (100). Decisional conflict scores of 25 or lower are associated with continuing with a decision, scores above 38 suggest a delay in decision making (O'Connor et al., 1998). The test-retest reliability coefficient has been demonstrated to be high at 0.81 (O'Connor, 1995) and internal consistency for total DCS score has been shown to be high (coefficients ranging from 0.78 to 0.92, O'Connor, 1995). The DCS is recommended as an outcome measure to assess the impact of decision in people with MS (Wilkie, Solari, & Nicholas, 2019).

Risk measures

The study assessed risk by following the risk assessment methodology of a previous study (Glanz et al., 2016; See Appendix M). This consisted of the following measures, presented to the patient in one risk questionnaire:

Risk attitude/Risk propensity

1) Single-item measure of risk orientation (Maestas & Pollock, 2010). This measure asks patients to rate their overall comfort with taking risks from extremely comfortable to extremely uncomfortable. A score of 1 or 2 indicates a risk seeking attitude, a score of 3, 4 or 5 indicates a risk neutral attitude and a score of 6 or 7 indicates a risk adverse attitude. The test-retest reliability of the measure is .94 in a lab setting and .69 in an internet survey (Maestas & Pollock, 2010). It has been validated against the 32 item ‘everyday risk-tasking inventory’ and performs as well as the RPS scales and other gamble measures (Maestas & Pollock, 2010).

2) Risk Propensity Scale (RPS; Meertens & Lion, 2008). This is seven-item self-report measure of an individual’s general tendency to take risks. It consists of 7 items that tap into different aspects of risk taking. Patients are asked to rate each item on a 9-point scale (ranging from 1, totally disagree to 9, totally agree), apart from the last item, which is rated on a scale from risk avoider (1) to risk seeker (9). Higher scores indicate higher risk seeking tendencies. The RPS has demonstrated good internal reliability and test-retest reliability coefficients (Cronbach’s alpha .80; Meertens & Lion, 2008).

3) A standard gambling scenario. This scenario asks patients to consider a new drug for MS which promises no new relapses or worsening of MS symptoms, but stipulates that it could cause death. Participants are asked to indicate the likelihood that they would take the new drug if the risk of death was 1:2, 1:10, 1:100, 1:1,000, 1:10,000 and 1:100,000.

Risk perception

1) Patients are asked to estimate the likelihood of becoming wheelchair-bound over the short- (two years), medium- (five years) and long-term (10 years) on a five-point scale (ranging from extremely unlikely to extremely likely).

2) Patients are asked to estimate the likelihood of minor and serious side effects associated with a range of medications commonly prescribed MS drugs.

Decision-making under ambiguity

Iowa Gambling Task (IGT; Bechara et al., 1994) is used to evaluate learning and decision making under ambiguous conditions where the risk is not explicitly explained to the patient and the ability to learn which options are more advantageous is required. Patients have to choose from four decks of cards in 100 trials and win or lose certain amounts of fictitious money. Two decks are disadvantageous in the long term; associated with immediate high gain but higher unpredictable future losses and two decks are advantageous in the long term because they provide low immediate gain but lower unpredictable future losses. As these rules are not explained to patients, they need to learn to choose from the more advantageous decks. Decision-making under

ambiguous conditions has been reported to be impacted in MS (Neuhaus et al., 2018). The Iowa Gambling Task was downloaded from The Psychology Experiment Building Language (PEBL) website (<http://pebl.sourceforge.net>). The Iowa Gambling Task is one of the most widely used tests in the PEBL battery (Mueller & Piper, 2014), used in many contexts and has been shown to be valid (Piper, Mueller, Talebzadeh, & Jung Ki, 2016).

Sample Benchmarking

Some of the measures and questionnaires included in the study are done so for reasons of benchmarking the sample. That is, to ensure that the sample is typical of other published samples.

Cognitive tests

The Brief International Cognitive Assessment for MS (BICAMS; Langdon et al., 2012) was used as a screening tool to identify cognitive impairment in patients with MS. It includes the Symbol Digit Modalities Test (SDMT), the learning trials of the California Verbal Learning Test II (CVLT-II) and the learning trials of the Brief Visuospatial Memory Test Revised (BVMT-R). The BICAMS is considered the gold standard cognitive screen to be used for people with MS (Corfield & Langdon, 2018).

SDMT (Smith, 1982; See Appendix N) is a test of Information Processing Speed. In this test symbols are paired with specific numbers in a key at the top of the record sheet. The record sheet contains symbols only, the number pairing is left blank. Participants are required to vocalise the numbers that correspond to the symbols as fast as possible.

There is an initial practice set of 10 items to ensure that participants understand what to do. A total score is calculated from the number of correct responses within 90 seconds. The oral element of the task ensures that fine motor skills are not a confounding variable. The test-retest reliability coefficient has been reported to be 0.97 (Benedict, 2005) and it is highly sensitive to detecting cognitive impairment in MS (Lopez-Gongora, Querol, & Escartin, 2015).

The CVLT-II (Delis, Kramer, Kaplan, & Ober, 2000; See Appendix O) measures episodic verbal learning and memory. The CVLT-II is a list comprising of 16 words, of four different categories. The list is read out at a rate of one word per second and the participant is asked to respond with as many words as they can recall. The list is read five times over five trials, with a maximum score of 16 per trial. A total score over the five trials is calculated, with a maximum total score of 80. It has been shown to be a valid test of verbal memory in MS (Stegen et al., 2010).

The BVMT-R (Benedict, 1997; See Appendix P) is a test of visual memory. Participants are presented with an array of 6 geometric figures for 10 seconds. After 10 seconds the stimulus sheet is removed and participants are given a blank piece of paper and asked to draw the shapes as accurately as they can and in the same position as they were on the stimulus sheet. This is repeated for 3 trials. One point is allocated for accurate drawing and one point for accurate placement (a total of 2 points per figure). Each trial has a potential score of 12, therefore a total maximum score is 36. The psychometric properties of the BVMT-R have been demonstrated to be good (Gaines, Gavett, Lynch, Bakshi, & Benedict, 2008).

The Wechsler Test of Adult Reading (WTAR; Wechsler, 2001; See Appendix Q) is a brief measure used to predict premorbid IQ. It consists of 50 irregular English words which participants are required to read aloud. Each correctly pronounced word is recorded. The raw score can be transformed to an age-adjusted standard score which is then used to predict IQ. WTAR scores have been found to be highly correlated with measures of verbal IQ ($r = .75$) and full scale IQ ($r = .73$) (Strauss, Sherman, & Spreen, 2006).

Questionnaires

The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983; See Appendix R) was used to assess affective MS symptoms. The HADS is a widely used measure of emotional distress and has two subscales measuring anxiety and depression, each comprising of seven items. Each item has response options ranging from 0 (not at all) to 3 (very much), with higher scores suggesting higher symptom severity. The maximum score for each subscale is 21 points. Patients scoring above 11 points on a subscale are considered to have a clinical level of anxiety or depression. A score between 8 and 10 on a subscale indicates borderline anxiety or depression. The HADS has demonstrated good internal consistency (Honarmand & Feinstein, 2009). Previous research has highlighted its sensitivity to depression and anxiety in MS (Watson, Ford, Worthington, & Lincoln, 2014).

The Fatigue Severity Scale (FSS; Krupp, LaRocca, Muir-Nash, & Steinberg, 1989; See Appendix S) is a nine-item self-report questionnaire originally developed for people

with MS. It comprises of nine items scored on a seven-point likert scale (1=strongly disagree; 7=strongly agree) and takes between 2-5 minutes to administer. It asks patients to rate their psychological or physical fatigue in the past seven days. A mean score is calculated and people scoring 5 or higher are deemed to have severe fatigue. The FSS has shown to be valid measure (Amtmann et al., 2012), with high internal consistency and high test-retest reliability (Learmonth, Moti, Sandroff, & Cadavid, 2013).

Demographics

Patient age, gender, ethnicity, level of education, employment status, years since MS diagnosis, EDSS and current DMD were collected on a questionnaire at the start of the experiment.

3.3.9. Procedure

The Consultant Neurologist or the Specialist MS Nurse at the hospital assessed patients for eligibility. If patients were interested they were given a information sheet and consent form, both approved by the NHS. Following providing consent, patients were seen at the hospital or at their home. The experiment took approximately one and a half hours to complete. Initially the researcher collected demographics and presented a visual acuity scale.

Patients were then shown the hypothetical disease. The researcher read the hypothetical disease out to the patient and the patient was given a hardcopy to consult during the presentation not throughout the understanding questions. The researcher then referred to

the allocated participant number referring to the randomisation number which referred to the order in which the patient would receive the BRIMMS and standard, as well as the order in which the treatments would be presented. It was ensured that all treatment combinations were represented equally, controlling for variation.

Patients were asked to imagine that they were at the early stages of the fictitious disease at which point only two treatments were offered (this was asked at the start of both the BRIMMS and the standard condition). They were then informed that the purpose of the session was for them to decide whether they would take one of the treatments for the hypothetical disease. Patients were not told whether they were receiving the BRIMMS or the standard condition.

Patients were asked comprehension questions after learning the risks and benefits of each treatment. Once patients had been presented with both treatments in any one condition, they were asked to make a decision on treatment (assessed using the DCS). Participants were then given three feedback questions, one of which assessed perceived understanding.

Patients were then given the measures to assess risk, premorbid IQ, cognition, fatigue, anxiety and depression (Figure 5).

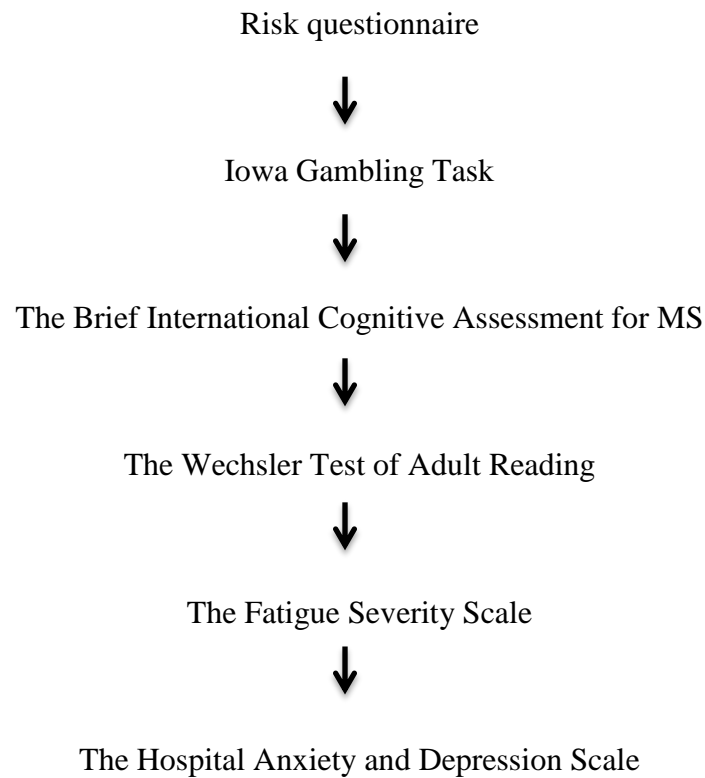


Figure 5. Order of risk measures and benchmarking variables

3.3.10. Statistical analysis

All statistical analyses were conducted using IBM SPSS 21.0 (IBM Corp; Armonk, New York, USA). A within-subjects ANOVA assessed the impact of condition on patient understanding and confidence in decision making. Pearson product-moment correlations examined the relationship between understanding/certainty in treatment decisions and anxiety, depression, fatigue, and cognitive impairment. Pearson product-moment correlations examined the relationship between self-reported risk attitude, risk perception and propensity to take risks and patients' understanding and certainty in

treatment decision. Due to carrying out multiple corrections, a level of $< .01$ was accepted as significant in order to guard against type 1 errors. In addition to an ANOVA, an ANCOVA was used to assess the impact of condition on patient understanding due to significant associations between fatigue, depression and anxiety and patient understanding. Therefore, fatigue, depression and anxiety were entered as covariates in this analysis. A cognitive composite score was created for each participant. The scores for the CVLT-II, SDMT and the BVMT-R for each participant were transformed into z-scores and then added together in order to create the composite score. This composite score was entered as a covariate. People with MS can have difficulties in a range of cognitive domains. The general cognitive impairment score allows analysis with one statistical test utilising one cognitive summary variable (Goverover et al., 2016). To analyse each of the three cognitive scales would have increased the number of tests and reduced power.

3.4. Results

3.4.1. Exploratory Data Analysis

Due to constraints of time, patient recruitment was somewhat slower than expected (see Figure 6). A total of 26 patients were analysed in the study, with no missing data. The data was examined to determine if the assumption of normality was met, as required for the use of parametric tests. A cut off of ± 2.58 ($p > .01$) was considered for kurtosis and skew as recommended by Tabachnick & Fidell (2013). The distribution of the data was considered normal. When considering outliers, scores were checked to ensure that they were not $3SD \pm \text{mean}$.

3.4.2. Demographic and Clinical Variables

Participant demographics (see Appendix U) and clinical variables (see Appendix V) were in line with previously reports in the literature. Participants age was in line with previously reported studies (Bichuetti et al., 2018; Bsteh et al., 2017; Kopke et al., 2017; Giordano et al., 2018). The ratio of male/female is consistent with published MS prevalence data (Mackenzie, Morant, Bloomfield, MacDonald, & O’Riordan, 2014). The mean IQ was average (103). In the general population, 50% of individuals have an IQ that falls between 90-109 (Wechsler, 2014). This suggests that participants in the current study are representative of the general MS population.

The means on the HADS are consistent with previously published means in the MS population (Pais-Riberio, Martins da Silva, Vilhena, Moreira, Santos, & Mendonca, 2018). Average age at diagnosis, EDSS scores and FSS score were in line with previous reports in the literature (Rejak, Jackson, & Giovannoni, 2010; Bichueti et al., 2018; Heesen et al., 2017; Kroencke, Lynch, & Denney, 2000).

10 (39%) participants were impaired on the SDMT, 7 (27%) were impaired on the CVLT-II and 8 (31%) were impaired on the BVM-T-R (see Appendix W). When comparing the sample means with published norms, the current sample is consistent with previous norms (Orchard, Giovannoni, & Langdon, 2013).

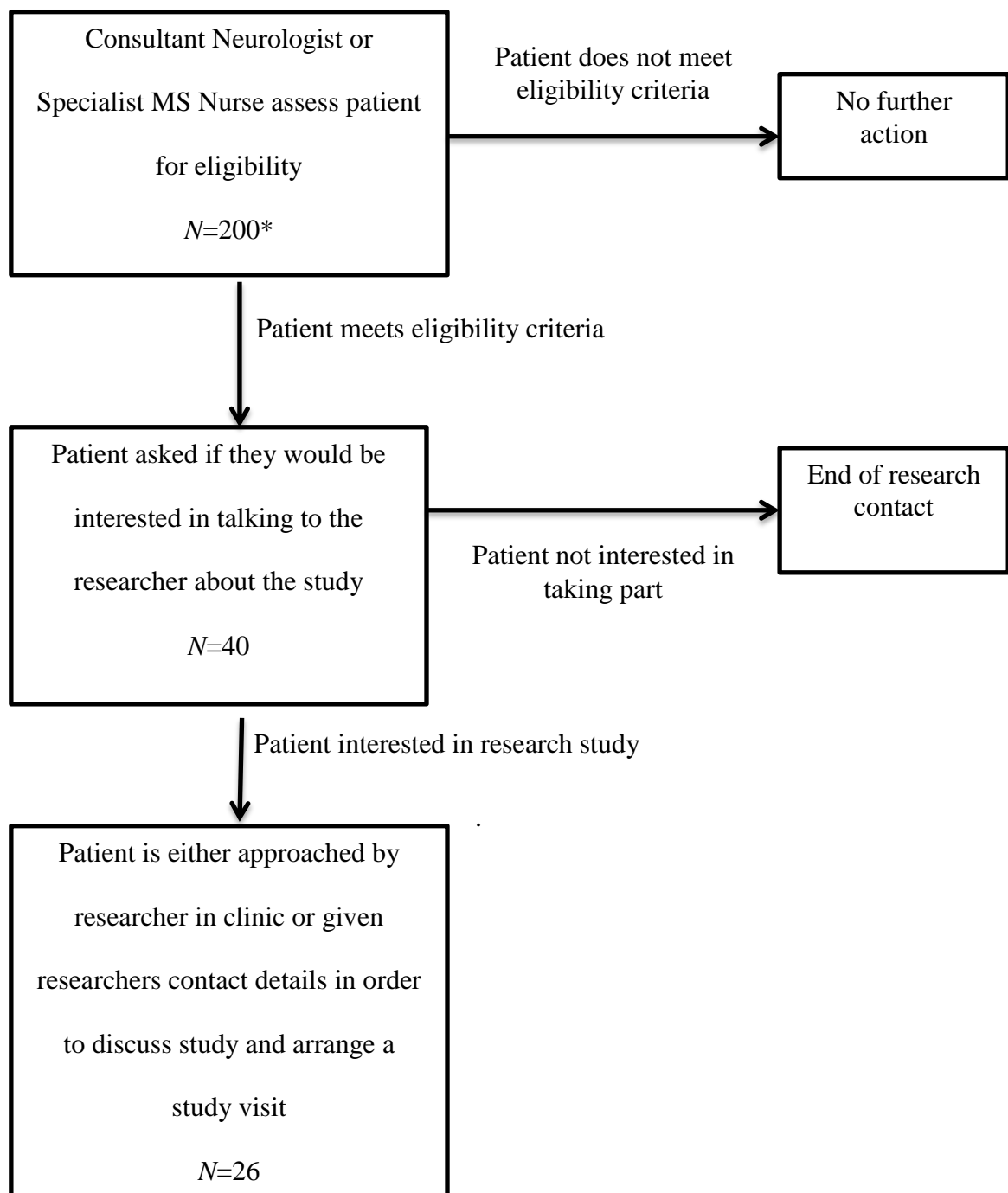


Figure 6. Recruitment pathway

*(N is an estimation)

3.4.3. Associations between clinical characteristics, cognition and outcome measures

As expected confounding variables were significantly inter-correlated, consistent with previously published work (See Appendix T; Skerrett & Moss-Morris, 2006).

A Pearson product-moment correlation was conducted to examine the relationship between each of fatigue, anxiety, depression, cognition and understanding score. There was a significant negative correlation between depression and BRIMMS understanding, that is, higher level of depression were associated with lower understanding scores on the BRIMMS ($r(24) = -.57, p = .002$). There was a significant negative correlation between anxiety and BRIMMS understanding, that is, higher levels of anxiety were associated with lower understanding scores on BRIMMS ($r(24) = -.79, p < .001$). There was a significant negative correlation between fatigue and BRIMMS understanding, that is, higher level of fatigue were associated with lower understanding scores on BRIMMS ($r(24) = -.41, p = .039$). There was no significant correlation between cognition and understanding ($r(24) = .38, p = .054$).

A Pearson product-moment correlation was conducted to examine the relationship between each of fatigue, anxiety, depression, cognition and decisional conflict. There were no significant associations between either fatigue ($r(24) = .12, p = .549$), depression ($r(24) = .15, p = .457$), anxiety ($r(24) = .01, p = .982$), cognition ($r(24) = -.18, p = .372$) and consultation as usual DCS score. There were no significant associations between fatigue ($r(24) = .08, p = .682$), depression ($r(24) = .34, p = .086$),

anxiety ($r(24) = .15, p = .470$), cognition ($r(24) = .18, p = .376$) and BRIMMS DCS score.

3.4.4. The effect of BRIMMS protocol and standard consultation on patients' understanding

A repeated measures ANOVA was carried out on the data. Mean scores for patients understanding are presented below (Table 6). Higher mean scores indicate greater understanding of treatment information. The mean difference between conditions was 24.23. Using the Greenhouse-Geisser correction, results showed that this difference was significant, $F(1,25) = 3388.83, p < .001$, 95% CI (23.372-25.088)); an overall effect size of 0.99 (partial η^2) showed that 99% of the variation in error scores can be accounted for by condition. Anxiety, depression and fatigue were co-varied together in the ANOVA. The effect of condition remains significant after co-varying anxiety, $F(1,22) = 13.28, p = .001$, but not depression, $F(1, 22) = .44, p = .517$ or fatigue, $F(1,22) = .35, p = .558$.

3.4.5 The effect of BRIMMS protocol and standard consultation on patients' decisional conflict

A repeated measures ANOVA revealed that there was a significant effect of condition on patients' decisional conflict, $F(1,25) = 10.78, p = .003$. Mean scores for patients' decisional conflict are presented below (Table 7). Lower scores indicate reduced

decisional conflict. The BRIMMS protocol was associated with lower decisional conflict.

3.4.6. The effect of BRIMMS protocol and standard consultation on patients' feedback

A repeated measures ANOVA revealed no significant effect of consultation on patient feedback, $F(1,25) = .94, p = .339$. Higher mean scores indicate more positive feedback (Table 8).

Table 6

Mean scores for patient understanding across both conditions

Condition	Max score	\bar{x} (SD)	Confidence interval (95%)	Minimum score	Maximum score
BRIMMS protocol	30	27.58 (1.67)	26.90-28.25	25	30
Standard consultation	30	3.35 (1.29)	2.82-3.87	2	6

Table 7

Mean scores for decisional conflict across both conditions

Condition	Max score	\bar{x} (SD)	Confidence interval (95%)	Minimum score	Maximum score
BRIMMS protocol	100	24.21 (14.91)	18.19-30.24	0	58
Standard protocol	100	38.28 (17.32)	31.28-45.27	6.3	83

Table 8

Mean scores for patient feedback across both conditions

Condition	Max. total score	\bar{x} (SD)	Confidence interval (95%)	Minimum score	Maximum score
BRIMMS	10	7.22 (2.07)	6.4-8.1	2.5	10
Standard	10	6.55 (2.59)	5.5-7.6	1.7	10

3.4.7. Associations between risk measures and decisional conflict score and/or understanding

On a single-item measure of risk orientation the mean score was equal to the middle of the scale, indicating a risk neutral attitude ($M = 4$; $SD = 1.92$; Table 9). Using the RPS, the mean (SD) risk propensity summary score was 3.70 (1.84), indicating an overall aversion to taking risks. On the IGT mean total score was 13.85 ($SD = 31.76$).

Using a standard gamble scenario, individuals reported the likelihood of taking a new MS drug given the probability of a fatal side effect (See Table 10). 4% of participants indicated they were likely to take the drug if the risk of death was 1:2. The proportion increased to 27% if the risk of death was reduced to 1:1,000, and to 54% if the risk of death was 1:100,000. 23% of participants indicated that they were unlikely/extremely unlikely to take the drug even if the probability of a fatal side effect was 1:100,000.

A Pearson product-moment correlation was conducted to examine the relationship between risk measures and decisional conflict and also understanding score. There were no significant associations between these variables. There were no significant associations between single-measure of risk orientation ($r(24) = .04$, $p = .840$), RPS ($r(24) = -.01$, $p = .952$), mean net score on Iowa gambling task ($r(24) = -.01$, $p = .973$) and BRIMMS DCS score. There were no significant associations between single-measure of risk orientation ($r(24) = .12$, $p = .545$), RPS ($r(24) = .16$, $p = .424$), mean net score on Iowa gambling task ($r(24) = -.00$, $p = .987$) and BRIMMS Understanding score.

Table 9

Descriptive statistics for risk measures

Measure	Maximum total score	\bar{x}	SD	Minimum	Maximum	Confidence interval (95%)
Single-measure	7	4.00	1.92	1	7	3.2-4.8
RPS	9	3.70	1.84	1	7.1	3.0-4.4
Mean net score	-	13.85	31.76	-40	72	1.0-26.7

Table 10

Results from standard gamble scenario

	Extremely unlikely <i>N</i> (%)	Unlikely <i>N</i> (%)	Neither likely nor unlikely <i>N</i> (%)	Likely <i>N</i> (%)	Extremely likely <i>N</i> (%)
1 in 2	24 (92)	-	1 (4)	1 (4)	-
1 in 10	22 (84)	2 (8)	-	1 (4)	1 (4)
1 in 100	20 (77)	3 (11)	1 (4)	1 (4)	1 (4)
1 in 1,000	16 (61)	2 (8)	1 (4)	6 (23)	1 (4)
1 in 10,000	8 (31)	6 (23)	2 (8)	5 (19)	5 (19)
1 in 100,000	5 (19)	1 (4)	6 (23)	7 (27)	7 (27)

3.5. Discussion

The current study aimed to confirm previous findings that BRIMMS is superior to standard consultation in improving patients' understanding of treatment risks and benefits and reducing patients' conflict regarding treatment decisions (Reen et al., 2017b). Furthermore, it aimed to expand on previous research by investigating how self-reported and objective risk attitude, risk perception and propensity to take risks relates to patient understanding of treatment risks and benefits as well as certainty in treatment decisions. The influence of risk perception and uncertainty on treatment decisions have been identified as neglected research topics (Webb et al., 2018). Furthermore, risk perception is considered critical in determining health behaviour (Ferrer & Klein, 2015).

3.5.1. Hypothesis 1: The BRIMMS protocol would improve patients' understanding of treatment risks and benefits compared to standard consultation

These results confirm previous findings that BRIMMS improved understanding compared to standard consultation (Reen et al., 2017b). Patients' understanding of treatment risks and benefits was significantly better on the BRIMMS compared to standard consultation. However, it is important to note that anxiety, depression and fatigue were significantly associated with understanding scores on the BRIMMS. When these variables were co-varied in the ANOVA, the effect of condition on understanding was no longer significant, when depression and fatigue were accounted for. Therefore, the differences in understanding scores may be explained by either fatigue or

depression. However, depression and fatigue are part of the condition of MS and therefore these findings are not a reason to suggest that BRIMMS is unhelpful for patients with these symptoms (Thompson et al., 2018).

3.5.2. Hypothesis 2: The BRIMMS protocol would reduce patients' conflict regarding treatment decisions compared to standard consultation

The second hypothesis was supported by the findings. The BRIMMS protocol was associated with significantly lower decisional conflict scores compared to standard consultation. This suggests that patients felt more informed, more confident in their treatment decision and clearer about their values. The results confirm previous findings (Reen et al., 2017b) and are in line with previous research that reports improved satisfaction and lower decisional conflict when patients partake in shared decision-making (Shay & Lafata, 2015). The observed power reported by SPSS was 0.88, which suggests that the study was sufficiently powered to detect difference in the DCS despite the small sample size.

3.5.3. Hypothesis 3: The BRIMMS would be rated more positively by patients than the standard consultation

The hypothesis was not supported by the findings and therefore is not in line with previous research (Reen et al., 2017b). Whilst not actively seeking feedback, the researcher noted some spontaneous comments from patients, whilst they deliberated on what feedback score to give. The qualitative feedback outlined as follows may explain

the lack of difference in feedback scores. A few patients mentioned that they preferred the information when it was presented as percentages (as in the standard consultation condition). The comments regarding the graphs in the BRIMMS condition were variable, some patients liked them, whereas others thought that they were unnecessary. A couple of patients thought that the BRIMMS had too many numbers and preferred the more simple presentation of the standard consultation. Conversely, a few people mentioned finding the graphs and lay out of the BRIMMS slightly patronising. It was observed that patients giving this feedback were usually those who found it easier to understand numbers. This is important information that would need to be taken into account if the BRIMMS was rolled out to patients in the clinical setting. It would be useful to explain this concept in the standardised instructions for the BRIMMS, for example, explaining that some people might find the information easier to understand than others.

3.5.4. Hypothesis 4 & 5: Self-reported risk attitude (single-measure of risk orientation), perception (RPS) and propensity to take risks (IGT) will predict patient understanding & Hypothesis 5: Self-reported risk attitude (single-measure of risk orientation), perception (RPS) and propensity to take risks (IGT) will predict patient decisional conflict scores

Both hypotheses were not supported by the findings. There were no associations between risk measures and understanding/decisional conflict scores. This could be due to the small sample size of the study and therefore insufficient power in order to detect associations. A post-hoc power analysis for Pearson correlation was conducted in G*

Power to determine a sufficient sample size with an alpha of 0.05, a power of 0.80, and a large effect size ($p = .5$), the determined sample size was 29, where as the collected sample size was 26, reducing the power to .77.

The results related to hypotheses four and five are interesting given that the literature suggests people with MS have difficulties making decisions under risk (Farez et al., 2014) and are generally risk averse which may have implications for decision making regarding treatments.

Despite the lack of associations between risk measures and understanding/decisional conflict scores, it is important to consider the context of the risk findings with previous research. Patients appeared to be risk neutral on the single measure of risk attitude which is in line with previous research (Glanz et al., 2016). The Risk Propensity Scale indicated that patients had an overall aversion to taking risks issues to health and safety, which reflects previous findings (Glanz et al., 2016). Mean total IGT score was in line with previous reports in the literature (Farez et al., 2014).

In terms of risk perceptions, 31% of patients reported the risk of their MS worsening over the next 2 years was likely/extremely likely, and 46% and 57% at 5 and 10 years respectively. These estimates are higher than previous reports (Glanz et al., 2016).

3.5.5. Limitations

The findings should be interpreted with caution given a number of limitations. Firstly, a medium effect size was used in the power calculation analysis, in hindsight it would have been more suitable to use a small effect size as a more conservative estimate.

Due to the design of the study, (the fact that the same hypothetical disease and two treatments were used in both formats) it is possible that there may have been some interference. The study would have benefited from a more robust design with two different hypothetical diseases and four different hypothetical treatments. This would have ensured that every patient had learnt about two diseases, each with two different drugs, therefore reducing the possibility of interference from previous understanding or misunderstanding. It may also have been beneficial to administer the other measures between conditions in order to provide a break between conditions and reduce the likelihood of a carryover effect. However, conditions and order of treatments were counterbalanced in an effort to reduce systematic bias from order effects on BRIMMS protocol and standard consultation format presentations.

The difference in length of presentation between the BRIMMS and the standard condition was not controlled for. This could have meant that the participants were more fatigued in the BRIMMS condition, and therefore could remember less information; however the longer length could also mean that they had longer to think about the information being presented to them and this extended exposure increased remembering.

The use of hypothetical disease and treatments raises the possibility that the findings may not apply to the understanding of real DMD risks and benefits, in that the information which was not personally relevant. This may have reduced patients emotional connection to the information and caused them to be less engaged. However, the hypothetical disease and treatment profiles were aligned closely with the risks and benefits of real DMDs.

Studies aiming to address these methodological difficulties have found that hypothetical diseases are an accepted methodology for exploring risk in MS patients (Bruce et al., 2018). Other methodologies have included presenting patients with five attributes of a DMD: relapse prevention, disease progression prevention, side-effect risk, route of administration and frequency of administration (Sempere et al., 2017). A five-card game was used to assess preferences, where patients were then asked to rank the attributes from most preferred to least preferred. It was confirmed that this was a feasible way to assess preferences in MS patients. Alternatively, one study assessed attributes by asking a focus group to compile a list (Kremer, Evers, Jongen, & Hilgsmann, 2018). This information was then collated into a survey with several choice answers (from best to worst) and given to a larger patient group. A strength of this study in using a focus group means that patients' perspectives were directly assessed, rather than relying on a set of attributions obtained from literature or through discussions with HCPs. It may be that a range of assessments would have strengthened the ecological validity of this study, had time allowed.

Side effect severity appears to impact decision-making regarding DMD; patients' likelihood of taking a DMD systematically decreased as the efficacy decreased and side effect severity increased (Jarmalowicz et al., 2017). The results suggest that information on severe side-effects should be presented separately to mild and moderate side-effects. Although our design did not systemically vary severity of side effects, the way the information was presented was closer to the experience a patient would have in a real clinic decision-making scenario.

Another limitation is the fact that the BRIMMS and standard consultation were not delivered by a MS health professional. Therefore, the presentation of the information was not identical to the experience as it would be in the clinic. It is important to consider how patients may interact differently if information is presented by a nurse or neurologist in a clinical setting, and they are able to ask questions. Furthermore, patients did not have any prior knowledge of the information presented, this means that they were unable to research or form their thoughts about it, which differs from what would happen in reality. Previous research has documented that people with MS use the internet as a means to search for information related to treatments (Lejbkowitz, Paperna, Stein, Dishon, & Miller, 2010). Furthermore, patients were asked to make a decision on the DCS immediately after seeing the treatment information, this is different to real clinical settings, where patients usually have more time to deliberate over and research their decision.

One of the key factors associated with shared decision making is patient preference (route of administration, work environment, lifestyle; Eskyte et al, 2019; Ben-Zacharia

et al., 2018). Patient preferences may influence DMD selection and adherence.

Discussions regarding patient preferences may help evaluate risk-benefit trade-offs associated with DMDs. Although the DCS touches on patient values, our study could have benefits from a more precise measure of patient preferences.

We did not include carers in our experiment. It is recognised that in a real clinical context, carers are likely to be involved in treatment decisions. We acknowledge the importance of including both patients and their family members when developing disease information and education materials (Mazanderani, Hughes, Hardy, Sillence, & Powell, 2019). This is an important area to think about for future research with the BRIMMS.

Another study looking at factors associated with MS patient preferences for DMDs found that monthly out-of-pocket cost was the attribute that was rated as having the most importance overall (Hincapie, Penm, & Burns, 2017). This suggests that our findings are not necessarily generalisable to other health care systems where patients must pay for all or part of their drug costs (which is likely to play a huge role in their treatment choices). Our MS participants were recruited from the NHS and do not have to pay for their DMDs.

It is possible that the study has selection bias, in that the attitudes and competencies of those that agreed to take part in the study may have differed from those that did not take part, which raises the possibility that the results may not be representative. For example, patients taking part may have been very interested in drug information and have more

background information/personal research on internet than the average patient; or patients with little understanding might have been embarrassed or ashamed to take part and hence less likely to volunteer. Another possible bias is that of the experimenter, the researcher may have indirectly influenced how the information was presented given that the researcher was not blinded to the condition that the patient received. It is important to take into account that environmental factors may have acted as confounds due to participants being assessed in their own homes. Participants were also tested at different times of day, which may have influenced the results in terms of differing fatigue levels. Although it is important to note that the sample in the current study was found to be a typical sample in terms of disease and demographic variables and the expected inter-correlations of confounding variables were found.

Another limitation is that fact that personality was not assessed or taken into account. Research shows that certain personality types are associated with various negative outcomes in MS (Strober, 2017). Specifically, ‘Type D’ personality was associated with more reports of fatigue, pain, depression, anxiety and worse disease management and adherence. It is likely that personality could have had an impact on the outcome measures in the current study.

3.5.6. Clinical Implications

The findings suggest that patients have incomplete understanding when treatment is presented in a standard consultation and BRIMMS has the potential to improve understanding of risks and benefits of DMDs. Implementing the BRIMMS in practice

could improve shared decision making, ensuring that patients choose a DMD with risks and benefits that they understand and consider acceptable. This could have an impact on adherence of DMDs, which is critical for long-term management of MS (Ben-Zacharia et al., 2018). Taking into account a patient's objective risk attitude, risk perception and propensity to take risks could be useful in determining patient characteristics in advance of the consultation during which the information is to be presented. It would mean that the presentation of the information could be amended to support the shared decision making process between patient and healthcare professionals.

3.5.7. Future research

Future research should aim to see if the finding that the BRIMMS improves understanding and confidence in decisions regarding treatment risks and benefits compared to standard consultation is replicable in a larger sample. The aim would be to validate the BRIMMS in a clinical setting. Future research would benefit from a more robust design, where each patient received two different hypothetical diseases with four different hypothetical treatments.

Future research, using a larger sample should measure risk alongside the BRIMMS in order to increase statistical power in order to detect any significant correlations risk attitude, risk perception, propensity to take risks and patient understanding scores regarding treatments as well as certainty in treatment decisions. Should an effect be found, risk orientation could be taken into account prior to discussions about DMDs in order to improve shared decision-making.

3.5.8. Conclusions

This study confirmed previous findings that the BRIMMS protocol is associated with better patient understanding of treatment risks and benefits and reduced decisional conflict, compared to standard consultation. However, differences in understanding scores may be explained by either fatigue or depression. It is recommended that the BRIMMS should be further evaluated and implemented in during consultation in a clinical setting. The study found no associations between risk measures and understanding or decisional conflict, this could be due to the study being slightly underpowered. Further research should measure risk alongside BRIMMS in a larger sample.

4. Integration, Impact and Dissemination

4.1. Integration

The aim of the thesis was to investigate MS patients' perceptions about the risks of MS and how this relates to their understanding of treatment risks and benefits and confidence in making these decisions. The systematic review provided an overview of the existing literature in regards to risk in relation to patients with MS. The systematic review provided an opportunity to summarise the literature in relation to patient's risk perception, risk attitude, risk tolerance/risk acceptance and risk knowledge. This provided the conceptual background for the empirical study, and was therefore critical in the integration of the two pieces.

The systematic review demonstrated that people with MS report uncertainty regarding the risks associated with DMDs. MS patients perceive the general risk to be higher than the risk they attribute to themselves. It was highlighted that elements of risk are related to treatment choice, for example, more risk seeking people were more likely to choose no treatment. Based on the findings of the systematic review it seemed necessary to take risk attitude, risk perception and propensity to take risks into account, in order to explore if there were any associations with understanding of treatment risks and benefits or certainty in treatment decision-making.

It is important to note that the majority of studies included in the systematic review did not measure cognition or mood, which are variables that could influence risk perception

and acceptance. It was vital to include measures of anxiety, depression, verbal memory, visual memory and processing speed in the empirical study in order to explore any associations with risk.

In addition to the risk measures, the empirical study aimed to replicate previous findings that the BRIMMS protocol improved patient understanding of DMD risks and benefits. This enabled a novel exploration of risk in MS, whilst aiming to confirm previous findings. The integration of the thesis is in line with policies and research that highlights the need for shared-decision making and solutions to enhance patient-physician communication, whilst providing patients with more autonomy in the management of their disease. It reflects the need to take into account patient preferences and characteristics prior to discussing DMDs in order to tailor communication effectively.

4.2. Methodological difficulties

4.2.1. Recruitment

Due to a number of reasons, recruitment was slower than expected, resulting in a final sample size of 26 patients. Despite there being an average of 20 patients per clinic, not all of them had a diagnosis of RRMS, or met the inclusion criteria for the study. It was often the case that those who were suitable and approached by the research nurse, did not provide consent to take part. This may have been partly due to the volume of patients in the clinic and the time available for the research nurse to explain the study. There was also a period that the research nurse involved in recruitment for the research

was absent, which may have impacted on the speed of recruitment. Furthermore, a few patients agreed to take part in the study and subsequently cancelled due to symptoms of MS, for example relapses or severe fatigue.

I responded to the recruitment difficulties by increasing my flexibility in terms of time of day and days of the week for patient visits. I also offered to see patients in their own homes. I made it a priority to contact patients that had shown an interest in the study, once they had provided consent for me to do so. Furthermore, I increased the number of clinics that I attended in an attempt to recruit more participants. My presence on the day of clinics enabled me to explain the study to patients and resulted in an increase in patient numbers. The research nurse was very helpful and ensured that she identified possible eligible patients prior to the clinic. This meant that she did not miss the opportunity to approach patients about the study.

4.2.2 Response to risk measures

Given the lack of associations between risk measures and understanding, I reflected on patients' responses to the risk measures. It is important to consider that some people appeared to get bored whilst completing the Iowa gambling task, often asking how much longer they had left on the task. I wondered whether this led patients to select the same deck (rather than changing decks according to their risk propensity) in the hope that the task would finish earlier or due to the fact that they were no longer engaged in the task. It is therefore possible that the validity of this task within this study could be

questioned. Perhaps the length of the task could have been explained in more detail, in order to set the time expectations for the patient.

The single-item measure of risk asked patients to rate their overall comfort with taking risks from extremely comfortable to extremely uncomfortable. A score of 1 or 2 indicates a risk seeking attitude, a score of 3, 4 or 5 indicates a risk neutral attitude and a score of 6 or 7 indicates a risk adverse attitude. I wondered whether it might be hard for people to think about risk in general. This may have led to people choosing the 'neither risk seeking nor risk adverse' option. However, this is unlikely given that this finding is reflective of previous research findings (Glanz et al., 2016).

In terms of general reaction to risk measures, a patient made commented that he feels that his risk attitude changes according to how he is feeling about his MS. This made me reflect on how risk as a concept is potentially likely to change rather than be something that is static. Many patients explained that the current risk that they were willing to take was dependent on their age. Some people said that being older meant that they would be willing to accept higher risks, than they would have done when they were younger; they mentioned 'I've got less to lose'. A couple of female patients explained that although they would technically want to accept higher risks they would not be willing to accept the risk due to the fact that their children were young and they would not want to risk not seeing the grow up. This made me think about how risk may be specific to stage in life or stage of disease. This made me consider the potential for future research to look at risk and understanding but with a follow-up period, so that risk and impact on DMD decision-making could be assessed at these different stages.

It is relevant to mention a research study, which aimed to explore the main factors affecting patients' preferences regarding MS treatment (Lee Mortensen & Rasmussen, 2017). Results demonstrated that although expected efficacy of DMDs was important to patients, this was modified by current well-being and Quality of Life related factors such as maintaining a positive self-image and a meaningful role that might be compromised by significant treatment burden. Authors link these findings to the Health Belief Model. Patients' treatment preferences involved balancing up their present and future Quality of Life in terms of the anticipated gains and losses. The Health Belief Model stipulates that personal perceptions about the perceived susceptibility and seriousness of the disease (including its impact on Quality of Life) and perceived threat as well as perceived benefits and barriers of a behavior, determine health behavior. It is important to say that these four main constructs are modified by variables such as cultural, education, past experience, motivation (Glanz et al., 2016). The importance that patients place on their current Quality of Life and role compared to long-term gains needs to be considered in decision-making. Of particular importance here is the finding that patients' DMD preference is in fact linked to age and disease progression and that parenthood may impact on the acceptability of risks and side effects (Wilson et al., 2015).

4.2.3. Defining structure for the systematic review

Supervision was vital in guiding the process of deciding on a succinct structure for the systematic review. It consisted of a process of deciding how to arrange the different concepts of risk. Whilst analysing the papers for the review I noticed that there was

quite a lot of overlap between the different concepts of risk that researchers discuss. I assume this is a reflection of the findings of the systematic review, in the sense that there is no unified way to assess risk or define risk in relation to MS. My supervisor recommended a book for me on completing a literature review and ‘releasing the research imagination’ to read; this helped me to organise my ideas and present it in a way to guide the audience through the review (Hart, 2018).

4.2.4. Lack of patient preference measures

Recent research has identified that a key factor associated with shared decision-making is patient preferences. This includes route of administration, work environment and lifestyle (Ben-Zacharia et al., 2018). Patient preferences may influence DMD selection and adherence. Discussions regarding patient preferences may help patients to evaluate risk-benefit trade-offs associated with DMDS. In hindsight, it would have been useful to include a measure of patient preferences in our study. Patients often mentioned that irrespective of the risks and benefits of the DMD, their treatment decision was based on route of administration (e.g. tablet, infusion or injection), treatment schedule and how the DMD would fit into their lifestyle. This highlighted the need to consider the decision process in the context of the patient’s life and the vital need to understand what motivates a person in their treatment decision-making. This is reflective of recent research, which highlights the importance of taking into account the contextual factors (clinical, social and psychological) of patients’ everyday lives when making decisions regarding initiating DMDs (Eskyte et al., 2019). Overall, involving MS patients in the

decision-making process is crucial for selecting the treatment that best suits the patients' objectives, preferences and lifestyles (Colligan, Metzlr, & Tiryaki, 2017).

4.2.5. Non-MS health professional

It is important to consider how patients may interact differently if the information was presented by a nurse or a neurologist in a clinical setting. The BRIMMS and standard consultation were delivered by a non-medical professional. It is likely that they would be able to answer specific questions that patients may have which would aid the decision making process. Whilst writing this section I considered the potential need to take into account cognitive biases or personality traits of the researcher/physician that administered the BRIMMS. A systematic review revealed how these biases or traits can affect clinical reasoning processes, which has implications for the management and treatment of medical conditions (Saposnik, Redelmeier, Ruff, & Tobler, 2016).

4.3. Service User Involvement

Service users were involved in the set-up of the study. Whilst I was writing my proposal, I outlined the design of the study and asked service users their perspectives about the concept of including risk. The feedback was very promising; service users felt that it was vital to take someone's risk characteristics into account in order to tailor the shared decision-making process for that person. In terms of writing a lay summary of the results, I will be asking a service user to read the summary before I send it to

patients who have requested it. This will ensure that the results are clear and relevant to patients with MS.

4.4. Impact

The patients within this study are representative of the MS population in terms of gender, age, premorbid IQ and other clinical variables. This suggests that the results can be generalised to the MS population as a whole. The beneficiaries of this research include MS patients, professionals working clinically with MS patients, those conducting academic research, as well as policy-makers and commissioners who are responsible for developing best practice around MS disease management.

I will discuss the areas in which I think the BRIMMS could have an impact clinically. There is scope for the communication between patients and HCPs to be improved. Risk knowledge is generally poor for MS patients (Giordano et al., 2018); patients generally underestimate DMD risks and overestimate DMD benefits (Reen, Silber, & Langdon, 2017a). A systematic review of qualitative and quantitative research, to understand the experiences of HCP and patient interactions in MS, highlighted that some patients felt they had a lack of choice and felt powerless in regard to their treatment and care (Soundy, Roskell, Adams, Elder, & Dawes, 2016). One study found that about half of patients believed that they were not completely involved in choosing a therapy (Lorefice et al., 2013). Research demonstrates that patients would like more involvement in decisions (Yeandle, Rieckmann, Giovannoni, Alexandri, & Langdon, 2018).

BRIMMS has the potential to increase patients' understanding of treatment risks and benefits. It would provide the opportunity for patients to be more involved in the decisions about their care. This is critical as increased patient involvement in disease management is likely to improve patient commitment to therapy. More patient involvement in decision-making is associated with improved outcomes, reduced healthcare utilisation and improved service quality. This could be measured through adherence, direct healthcare costs and HCP-patient relationship satisfaction.

The results offer important contributions to the clinical psychology literature and can be used to inform best practice regarding shared decision-making for the MS population. It is hoped that the study will lead to further research and implementation of BRIMMS within a clinical setting. For MS patients this has the potential to increase their understanding of DMD risks and benefits and make them feel more comfortable and confident in their treatment decision-making. If patients feel more comfortable with their decision and understand the risks and benefits, this is likely to lead to better drug adherence, which could lead to maintaining function for longer (Ben Zacharia et al., 2018). In terms of impact from the risk element of the empirical study, the lack of relation of DMD understanding to patient risk profile, provides no support for risk screening prior to presenting information in the clinic. Although, it must be noted that it is a small sample size and possibly underpowered.

The results provide professionals working with people with MS a tool that has the potential to aid in the shared decision making process. The impact for academic research is the hope that the study inspires academic researchers to replicate the study with a larger sample. In terms of the impact on policy makers and commissioners, it

may be beneficial to think about implementing the BRIMMS in practice in order to improve long-term outcomes. The study is relevant for public health policies; despite MS being a common neurological disorder, with effective DMDs, treatment adherence remains low. The BRIMMS has the potential to have an effect on treatment adherence. The findings compliment the research completed by the MS in the 21st Century Steering group, which is committed to advancing shared-decision making. The BRIMMS has the potential to enhance the quality of life of people with MS, in terms of reducing relapses.

It is important to consider the barriers that may influence the impact of this thesis. Some may argue that it would take longer to use the BRIMMS to communicate treatment risks and benefits than current practices that are in place. Future research could consider presenting BRIMMS on an iPad, this may increase the ease at which it could be used. In terms of affordability, the BRIMMS may help with adherence rates and in turn reduce relapse rates, which has a knock on effect for reduced utilisation of health resources. When considering how these benefits might be evidenced, the DSC could be used to measure patient satisfaction and decisional conflict. Perhaps there is a need for more studies examining the cost-effectiveness of decisional aids in terms of their effect on adherence rather than solely understanding.

4.5. Dissemination

4.5.1. Presentations

The preliminary results of the empirical study were presented in May 2019 at the Royal Holloway University of London third year Clinical Psychology Trainee presentation day. Attendees included clinical staff and Trainee Clinical Psychologists. The benefit of presenting to an academic audience allows the possibility that they may take forward the findings into their future projects. During discussions about my research, I was able to advise a fellow Trainee Clinical Psychologist in regards to the length of testing battery and recruitment strategy.

There is the potential to present the results at a patient support group meeting. I am aware that establishing a network with service users increases the impact that research can have. I appreciate and acknowledge the active role that service users have in making the impact of research happen. A patient who participated in the research independently set up a patient support group and presents on radio shows about her experience of MS. This attitude and enthusiasm would be invaluable in terms of generating impact from research.

4.5.2. Publications

Both the empirical study and the systematic review will be prepared for publication in academic journal. The systematic review will be submitted to the Multiple Sclerosis and

Related Disorders (MSARD). The MSARD was selected as it is an international journal and aims to enhance the practice of academics involved in the care of people with MS. It has an impact factor of 3.2. A shorter version of the empirical study will be submitted to Multiple Sclerosis Journal (MSJ) for review, this is a highly respected journal with an impact factor of 5.3. A brief summary of the empirical study will also be sent to participants that requested a summary. This is in line with Good Practice Guidance from the Health Research Authority (“Good Clinical Practice”, 2018).

4.6. Personal reflections

I found completing this research a very thought-provoking and exciting opportunity. I have always been interested in neuropsychology and was extremely keen to complete a project within the area. I was inspired by the fact that the results of the study would be clinically relevant. In deciding upon a thesis, it was important for me to pick a project in an area that I feel passionate about.

Furthermore, despite previously working with patients with a number of neurological conditions, I had not worked with people with Multiple Sclerosis. I was keen to complete my research with a new patient population. Working with MS patients whilst undertaking the research has further confirmed that I want to work in the area of neuropsychology as a qualified Clinical Psychologist.

During this project, I attended a pop-up event in London, organised by the charity, Shift.MS. The event was a private viewing of a short film on the invisible symptoms of

MS. MS is most often known for the effect that it has on mobility. However, it is also associated with symptoms that are less well known, sometimes referred to as invisible symptoms. They include, but are not limited to, fatigue, depression, anxiety, dizziness, cognitive problems, and pain. These symptoms can be incredibly frustrating and can have a severe effect on Quality of life and daily functioning, such as managing at work, keeping up with conversations and managing activities of daily living.

During the film, the symptoms are illustrated using doppelgangers and dance. My initial reaction to the short film was one of shock as the portrayal of some of the characters was fairly frightening. The film highlighted to me the fact that so often these hidden symptoms are under acknowledged. This knowledge was invaluable when completing my research study. It was helpful to think about how I would engage with patients with MS in the clinic or at home. One of the things that struck me was the importance of the film not only for the understanding for those without MS but for those with MS and the validation that it is perfectly normal to experience these hidden symptoms. Furthermore, this event was a useful opportunity for my supervisor to speak to her colleagues about the project that we were conducting.

Whilst conducting the research, I started my third year clinical placement in a neuro-rehabilitation setting. People with MS are faced with such uncertainties about the future, in terms of their symptoms, treatment and side effects of treatments. MS can impact on achieving life goals, job, income, relationships, social life and other daily living activities. Unsurprisingly, MS poses many psychological challenges in regarding to adjustment to MS as a diagnosis or the symptoms of the disease. I saw a few patients for

therapy for adjustment to MS work whilst I was on placement. This consisted of using the Cognitive Behavioural Therapy manual for adjustment to early stages of MS. This was a result of the randomised control Supportive Adjustment to MS trial (Moss-Morris et al., 2013). Interestingly 'early stage MS' refers to within 10 years of diagnosis. This was reflected in my work, as I saw people at with a range of years since diagnosis.

People often experienced distress years after a diagnosis, when their MS had progressed and was stopping them from doing the things they used to be able to do.

Whilst completing my research project alongside my placement, I was struck by the lack of psychological support that people had received in relation to their MS. I spoke to the research nurse about this and she explained that there is a lack of neuro-rehabilitation services in the geographical areas that the patients live. The nurse refers them to Improving Access to Psychological Therapies, or suggests that they self-refer. I wondered how adjustment, and the way that a person manages their diagnosis of MS or the disease in general, impacts on some of the risk measures. For example when asked the risk question about likelihood of disease progression, a few people explained that this is something they avoid thinking or speaking about. I wondered whether this may account for 38%, 27% and 35% selecting the 'neither likely nor unlikely' option for 2, 5 and 10 years, respectively. By selecting this option, patients are not stipulating either way. This is a concept that I feel is related to the illness representation theory, which emphasises the need to look at everyday beliefs and coping strategies for illness to understand treatment choices (Leventhal et al., 1997).

Whilst on my final placement, in a paediatric setting, I was co-supervising an Assistant Psychologist. She was completing a systematic review as part of her placement year for her university degree. Discussing her systematic review made me reflect on my own review. It also made me aware how much my self-reflexivity skills have developed since I started training.

Despite the drive for shared decision-making, and moving away from the paternalistic model (assuming a passive role for the patient) where the physician decides what DMD the patient should be on and expects the client to be compliant, many of the patients that I met said that they ‘just go with the DMD that the neurologist suggests’. Although it was not within the scope of the current study to explore this further, it made me think about the importance of how the medical professional explains the shared decision-making process. Highlighting the likelihood of better adherence with increased understanding and the need for people to be happy with their choice and accepting with the specific risks and benefits.

It seems appropriate to finish with my reflections in relation to a paper written by a member of the MS in 21st Steering group and MS health professionals, about patient involvement in treatment decisions. I feel that the BRIMMS is a tool that is in line with the Steering groups’ goal to develop solutions to enhance patient-physician communication, whilst providing patients with more autonomy in the management of their disease.

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6. Appendices

Appendix A

HRA Proportionate Review Confirmation of Ethical Approval (dated 19/06/18)



**Office for Research Ethics Committees
Northern Ireland
(ORECNI)**

Customer Care & Performance Directorate
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HSC REC B

**Please note: This is the
favourable opinion of the
REC only and does not allow you
to start your study at NHS sites in
England until you receive HRA
Approval**

19 June 2018

Miss Elizabeth Donnachie
Trainee Clinical Psychologist
Department of Psychology
Royal Holloway
Egham
TW20 0EX

Dear Miss Donnachie

Study title: Effect of risk propensity on understanding and decision-making regarding disease-modifying drugs in Multiple Sclerosis.
REC reference: 18/NI/0102
Protocol number: 1
IRAS project ID: 237342

Thank you for your letter of 12 June 2018, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a

Providing Support to Health and Social Care



request to defer, or require further information, please contact please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a **favourable ethical opinion** for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise). Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System, at www.hra.nhs.uk or at <http://www.rdforum.nhs.uk>.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 8 weeks after recruitment of the first participant. There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" above).

Approved documents

The documents reviewed and approved by the Committee are:

Document	Version	Date
Copies of advertisement materials for research participants [Leaflet]	1	04 April 2018
Covering letter on headed paper [Cover letter v1 12.06.2018 IRAS237342]	1	12 June 2018
Evidence of Sponsor Insurance or Indemnity (non NHS Sponsors only) [Evidence of sponsor Indemnity]	1	26 July 2017
IRAS Application Form [IRAS_Form_14052018]		14 May 2018
IRAS Checklist XML [Checklist_14052018]		14 May 2018
IRAS Checklist XML [Checklist_13062018]		13 June 2018
Letter from sponsor [Letter from sponsor]	1	19 April 2018
Other [Lone working policy v1 12.06.2018 IRAS237342]	1	12 June 2018
Participant consent form [Consent form]	1	01 March 2018
Participant Information sheet (PIS) [Patient Information sheet]	2	12 June 2018
Research protocol or project proposal [Proposal]	1	11 April 2018
Summary CV for Chief Investigator (CI) [CV for CI]	1	04 April 2018
Summary CV for supervisor (student research) [CV for supervisor]	1	25 February 2018
Validated questionnaire [BRIMMS]	1	30 April 2018
Validated questionnaire [Standard presentation]	1	30 April 2018
Validated questionnaire [Hypothetical disease]	1	10 May 2018
Validated questionnaire [Understanding questions (Vettinoli)]	1	30 April 2018
Validated questionnaire [Understanding questions Zafloxtrate]	1	30 April 2018
Validated questionnaire [Perceived understanding questions]	1	30 April 2018
Validated questionnaire [DCS]	1	29 April 2018
Validated questionnaire [BVMT-R Instructions]	1	30 April 2018
Validated questionnaire [BVMT-R form]	1	10 May 2018
Validated questionnaire [CVLT-II]	1	10 May 2018
Validated questionnaire [WTAR]	1	10 May 2018
Validated questionnaire [WTAR scoring sheet]	1	10 May 2018
Validated questionnaire [FSS]	1	10 May 2018
Validated questionnaire [Risk measures]	1	29 April 2018
Validated questionnaire [HADS]	1	10 May 2018
Validated questionnaire [SDMT Investigator sheet]	1	10 May 2018
Validated questionnaire [SDMT]	1	10 May 2018
Validated questionnaire [SDMT Instructions]	1	30 April 2018

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics

Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- ☐ Notifying substantial amendments
- ☐ Adding new sites and investigators
- ☐ Notification of serious breaches of the protocol
- ☐ Progress and safety reports
- ☐ Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: <http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance>

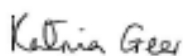
We are pleased to welcome researchers and R & D staff at our RES Committee members' training days – see details at <http://www.hra.nhs.uk/hra-training/>

18/NI/0102

Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely


pp:
Professor Patrick Murphy
Chair

Email: prs@hscni.net

Enclosures: "After ethical review – guidance for researchers" [SL-AR2]

Copy to: Ms Annette Lock
Ms Amanda Biddle
Dr Gary Brown

Appendix B

Letter of approval from Health Research Authority and Health and Care Research

(dated 09/07/18)



Miss Elizabeth Donnachie
Department of Psychology
Royal Holloway
Egham
TW20 0EX

09 July 2018

Dear Miss Donnachie



Email: hra.approval@nhs.net
Research-permissions@wales.nhs.uk

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title: Effect of risk propensity on understanding and decision-making regarding disease-modifying drugs in Multiple Sclerosis.
IRAS project ID: 237342
REC reference: 18/NI/0102
Sponsor Royal Holloway

I am pleased to confirm that [HRA and Health and Care Research Wales \(HCRW\) Approval](#) has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales?
You should now provide a copy of this letter to all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment.

Following the arranging of capacity and capability, participating NHS organisations should **formally confirm** their capacity and capability to undertake the study. How this will be confirmed is detailed in the *"summary of assessment"* section towards the end of this letter.

You should provide, if you have not already done so, detailed instructions to each organisation as to how you will notify them that research activities may commence at site following their confirmation of capacity and capability (e.g. provision by you of a 'green light' email, formal notification following a site initiation visit, activities may commence immediately following confirmation by participating organisation, etc.).

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed [here](#).

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?

HRA and HCRW Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) has been sent to the coordinating centre of each participating nation. You should work with the relevant national coordinating functions to ensure any nation specific checks are complete, and with each site so that they are able to give management permission for the study to begin.

Please see [IRAS Help](#) for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?

HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to [obtain local agreement](#) in accordance with their procedures.

What are my notification responsibilities during the study?

The document *"After Ethical Review – guidance for sponsors and investigators"*, issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The [HRA website](#) also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

I am a participating NHS organisation in England or Wales. What should I do once I receive this letter?

You should work with the applicant and sponsor to complete any outstanding arrangements so you are able to confirm capacity and capability in line with the information provided in this letter.

The sponsor contact for this application is as follows:

Name: Annette Lock

Tel: 01784 414388

Email: annette.lock@rhul.ac.uk

Who should I contact for further information?

Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is 237342. Please quote this on all correspondence.

IRA8 project ID	237342
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Yours sincerely

Maeve Ip Groot Bluemink
Assessor

Email: hra.approval@nhs.net

Copy to: *Annette Lock, Royal Holloway University London – Sponsor Contact*
Ms Amanda Bidle, Royal Free London NHS Foundation Trust – Lead R&D Contact

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	Version	Date
Copies of advertisement materials for research participants [Leaflet]	1	04 April 2018
Covering letter on headed paper [Cover letter v1 12.06.2018 IRAS237342]	1	12 June 2018
Covering letter on headed paper [Response to assessment queries]	1	05 July 2018
Evidence of Sponsor Insurance or Indemnity (non NHS Sponsors only) [Evidence of sponsor Indemnity]	1	26 July 2017
HRA Schedule of Events	1 (HRA final)	09 July 2018
HRA Statement of Activities	1 (HRA final)	09 July 2018
IRAS Application Form [IRAS_Form_14052018]		14 May 2018
Letter from sponsor [Letter from sponsor]	1	19 April 2018
Other [Lone working policy v1 12.06.2018 IRAS237342]	1	12 June 2018
Participant consent form [Consent form]	1	01 March 2018
Participant information sheet (PIS)	3	05 July 2018
Research protocol or project proposal [Proposal]	1	11 April 2018
Summary CV for Chief Investigator (CI) [CV for CI]	1	04 April 2018
Summary CV for supervisor (student research) [CV for supervisor]	1	25 February 2018
Validated questionnaire [BRIMMS]	1	30 April 2018
Validated questionnaire [Standard presentation]	1	30 April 2018
Validated questionnaire [Hypothetical disease]	1	10 May 2018
Validated questionnaire [Understanding questions (Vettinot)]	1	30 April 2018
Validated questionnaire [Understanding questions Zafloxtate]	1	30 April 2018
Validated questionnaire [Perceived understanding questions]	1	30 April 2018
Validated questionnaire [DCS]	1	29 April 2018
Validated questionnaire [BVM-T-R Instructions]	1	30 April 2018
Validated questionnaire [BVM-T-R form]	1	10 May 2018
Validated questionnaire [CVLT-II]	1	10 May 2018
Validated questionnaire [WTAR]	1	10 May 2018
Validated questionnaire [WTAR scoring sheet]	1	10 May 2018
Validated questionnaire [FSS]	1	10 May 2018
Validated questionnaire [Risk measures]	1	29 April 2018
Validated questionnaire [HADS]	1	10 May 2018
Validated questionnaire [SDMT Investigator sheet]	1	10 May 2018
Validated questionnaire [SDMT]	1	10 May 2018
Validated questionnaire [SDMT Instructions]	1	30 April 2018

Summary of assessment

The following information provides assurance to you, the sponsor and the NHS in England and Wales that the study, as assessed for HRA and HCRW Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England and Wales to assist in assessing, arranging and confirming capacity and capability.

Assessment criteria

Section	Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/consent documents and consent process	Yes	Changes have been made to the PIS by non-substantial amendment after the REC opinion to align them with HRA & HCRW Approval standards.
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	A Statement of Activities has been submitted and it is intended for this to be used as the contract between the Sponsor and NHS sites.
4.2	Insurance/indemnity arrangements assessed	Yes	[A76-3] Participants will be recruited from NHS sites so NHS indemnity will apply for the conduct of the research.
4.3	Financial arrangements assessed	Yes	No application for external funding has been made. There will be no financial provisions to the sites.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	No comments
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	No comments

Section	Assessment Criteria	Compliant with Standards	Comments
5.3	Compliance with any applicable laws or regulations	Yes	No comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	REC Favourable Opinion was issued by the HSC REC B REC.
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	No comments
6.3	Devices – MHRA notice of no objection received	Not Applicable	No comments
6.4	Other regulatory approvals and authorisations received	Not Applicable	No comments

Participating NHS Organisations in England and Wales

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.

There is one type of participating NHS organisation; therefore, there is only one site type.

The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England and Wales in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. Where applicable, the local LCRN contact should also be copied into this correspondence.

If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England and Wales which are not provided in IRAS, the HRA or HCRW websites, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net or HCRW at Research-permissions@wales.nhs.uk. We will work with these organisations to achieve a consistent approach to information provision.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and Wales, and the minimum expectations for education, training and experience that PIs should meet (where applicable).

Local Collaborator (LCs) are expected for this type of study. The LCs have been identified at the NHS sites and are listed in IRAS Form [Part C].

GCP training is not a generic training expectation, in line with the [HRA/HCRW/MHRA statement on training expectations](#).

IRAS project ID	237342
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HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken

Where arrangements are not already in place, research staff not employed by the NHS host organisation undertaking any of the research activities listed in the research application would be expected to obtain a Letter of Access based on standard DBS checks and occupational health clearance.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales to aid study set-up.

The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio.

Appendix C

Royal Free R&D: Letter of access (dated 13/09/18)



Royal Free Hospital
Pond Street
London
NW3 2QG

Tel: 020 3758 2000

13/09/2018

Dear Elizabeth Donnachie

Project ID: 11504 (Please quote in all correspondence)
REC Ref: 18/NI/0102
IRAS ID: 237342
Title: Effect of risk propensity on understanding and decision-making regarding disease-modifying drugs in Multiple Sclerosis

Letter of access for research

This letter should be presented to each participating organisation before you commence your research at that site.

In accepting this letter, each participating organisation confirms your right of access to conduct research through their organisation for the purpose and on the terms and conditions set out below. This right of access commences on 13/09/2018 and ends on 30/09/2019 unless terminated earlier in accordance with the clauses below.

As an existing NHS employee you do not require an additional honorary research contract with the participating organisation(s). The organisation(s) is/are satisfied that the research activities that you will undertake in the organisation(s) are commensurate with the activities you undertake for your employer. Your employer is fully responsible for ensuring such checks as are necessary have been carried out. Your employer has confirmed in writing to this organisation that the necessary pre-engagement checks are in place in accordance with the role you plan to carry out in the organisation(s). Evidence of checks should be available on request to Royal Free London NHS Foundation Trust.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving the organisation(s) permission to conduct the project.

You are considered to be a legal visitor to Royal Free London NHS Foundation Trust premises. You are not entitled to any form of payment or access to other benefits provided by Royal Free London NHS Foundation Trust or this organisation to employees and this letter does not give rise to any other relationship between you and Royal Free London NHS Foundation Trust or this organisation, in particular that of an employee.

While undertaking research through Royal Free London NHS Foundation Trust, you will remain accountable to your employer Camden and Islington NHS Trust but you are required to follow the reasonable instructions of your nominated manager in each organisation or those given on her/his behalf in relation to the terms of this right of access. Your nominated manager at Royal Free London NHS Foundation Trust is Dr Robert Brenner.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by Camden and Islington NHS Trust or this organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with Royal Free London NHS Foundation Trust policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with Royal Free London NHS Foundation Trust in discharging its duties under the Health and Safety at Work Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on Royal Free London NHS Foundation Trust premises. Although you are not a contract holder, you must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of a contract holder and you must act appropriately, responsibly and professionally at all times.

If you have a physical or mental health condition or disability which may affect your research role and which might require special adjustments to your role, if you have not already done so, you must notify your employer and each participating [Royal Free London NHS Foundation Trust] prior to commencing your research role at each site.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

The organisation(s) will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that the organisation(s) accept no responsibility for damage to or loss of personal property.

This letter may be revoked and your right to attend the organisation(s) terminated at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of the organisation(s) or if you are convicted of any criminal offence. You must not undertake regulated activity if you are barred from such work. If you are barred from working with adults or children this letter of access is immediately terminated. Your employer will immediately withdraw you from undertaking this or any other regulated activity and you **MUST** stop undertaking any regulated activity immediately.

Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

If your circumstances change in relation to your health, criminal record, professional registration or suitability to work with adults or children, or any other aspect that may impact on your suitability to

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Page 2 of 3

Dominic Dodd, chairman David Sloman, chief executive

conduct research, or your role in research changes, you must inform the organisation that employs you through its normal procedures. You must also inform the nominated manager in each participating organisation.

Yours sincerely



Neil Hubbard
Research Portfolio Manager
Royal Free London NHS Foundation Trust

cc: HR department of the substantive employer
PI Dr Robert Brenner

Appendix D

Participant Information Sheet



PATIENT INFORMATION SHEET

Effect of risk propensity on understanding and decision-making regarding disease-modifying drugs in Multiple Sclerosis

We would like to invite you to take part in our research study. This research study is being conducted as part of a DClinPsy project at Royal Holloway, University of London. Joining the study is entirely up to you, before you decide whether to take part it is important that you understand why the research is being done and what it would involve for you. Please take time to read this information, and discuss it with others if you wish. One of our team will go through the information sheet with you, if there is anything that is not clear, or if you would like more information, please ask us.

What is the purpose of the study?

People with Multiple Sclerosis are faced with complicated information about the risks and benefits of disease-modifying medications. Recently, a researcher developed a novel way to present treatment risks and benefits of disease modifying drugs to patients with MS. The current study will compare the novel way of presenting information with usual presentation in order to find out whether one method helps improve understanding and confidence in treatment decision making more than another. Furthermore, previous research has found that people with MS find decisions involving risk hard to make. Therefore, this study will investigate whether risk attitude and risk perception are related to understanding and certainty in treatment decision-making.

The aim of this study is to carry out a comparison of two methods of giving information with the hope of improving patients' decision making about treatments.

Why have I been invited?

You have been given this information because your clinical team think that the study might be suitable for you.

We are inviting 48 people to take part in the study. Clinical teams will refer people with MS to our research team. We then meet with each person to make sure that the research is appropriate for them and answer questions they may have. Each person who takes part will have a diagnosis of relapsing-remitting Multiple Sclerosis and be currently taking disease-modifying drugs.

Do I have to take part?

No, it is up to you whether or not you take part. If you do decide to take part, it will not affect the care you receive in any way. You can withdraw at any time, without giving a reason.

What will happen if I decide to take part?

You will meet with the researcher from the team to complete the study.

We will present you with medication information which is hypothetical but very similar to the risks and benefits of MS drugs. We will use two different methods of information giving when providing you with information about these pretend drugs. The order in which you receive the two different formats may influence your understanding (i.e. you may learn things from the first set that help you understand the second set of information). We will mix up the order in which different participants receive the two information formats. We will use a process called randomisation, which is a bit like tossing a coin, and relies on chance to decide each participant's particular order of formats. To measure your understanding, you will then be asked a few questions about the information you have received. You will also be asked to choose hypothetically between the two medications you were given and be asked a few questions about your confidence in that decision.

Before the study task, you will be asked to fill in some questionnaires about your mood, fatigue, memory, concentration and attitude towards risk to see how these factors may influence your understanding about medication risks and benefits.

The whole session may take around 2 to 3 hours. However, breaks will be given throughout the study if you feel uncomfortable or tired.

If the research study requires an additional journey to the clinic, reasonable travel expenses will be available if agreed in advance.

What are the potential benefits of taking part?

We aim to use the information we collect to design and promote better ways of presenting drug information to people with MS. You will have helped us do that.

What are the potential risks of taking part?

Potential risks include fatigue, since study sessions may last up to 3 hours. However, you may omit any questions you do not wish to answer and are encouraged to take regular breaks when taking part. Other similar studies have not encountered these problems.

How will my data be used and will my taking part in the study be kept confidential?

Royal Holloway, University of London is the sponsor for this study based in the United Kingdom. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Royal Holloway, University of London will keep identifiable information about you for 1 year after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information by contacting Professor Dawn Langdon, based at Royal Holloway, University of London.

The Royal Free will use your name, NHS number and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from Royal Holloway, University of London and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The Royal Free will pass these details to Royal Holloway, University of London along with the information collected from you and your medical records. The only people in Royal Holloway, University of London who will have access to information that

identifies you will be people who need to contact you to arrange your study visit or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

Royal Holloway, University of London will keep identifiable information about you from this study for 1 year after the study has finished.

Royal Holloway, University of London will collect information about you for this research study from The Royal Free. This information will include your name, NHS number, contact details and health information, which is regarded as a special category of information. We will use this information to contact you to arrange your study visit.

All of the data collected during the study will be kept confidential and will only be viewed by authorised researchers in the research team. The study forms you complete will not have your name on (we identify you with a unique study code), and will be kept in a locked cabinet in a locked room. When the results of the study are reported, participants who have taken part will not be identifiable in any way.

Your contact details will be retained at the end of the study in order to send you a summary of the findings of the study, if you express that this is something you would be interested in receiving.

What will happen to the results of the study?

We plan to present these results at educational conferences for neurologists and MS Nurses. We will intend to publish our findings in scientific journals which are read by the MS community. Your information will be anonymised in any publication and you will not be able to be identified.

Who is funding the study?

Royal Holloway, University of London.

Who has reviewed the study?

All studies that take part in the NHS are reviewed by an independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by the Health and Social Care Research Ethics Committee B (HSC REC B).

The research has also been approved by the Ethics Committee at Royal Holloway, University of London.

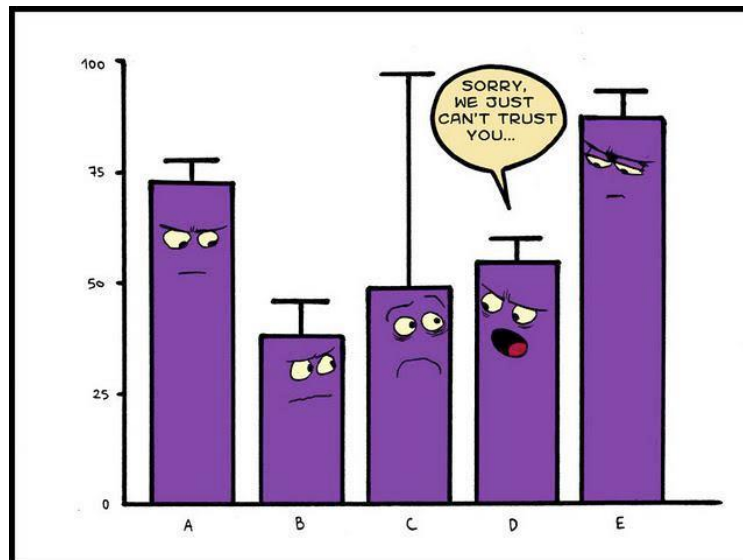
Contact details

If you have any questions about this study or would like more information about this project, please contact:

Elizabeth Donnachie
Trainee Clinical Psychologist
Elizabeth.donnachie.2016@live.rhul.ac.uk

If taking part in the study raises concerns about your symptoms or care, please contact:

Noreen Barker
MS Clinical Nurse Specialist
Noreen.barker@nhs.net
0207 317 7537



Volunteers needed for a study to make MS drug information easier to understand

We are looking for people with relapsing remitting MS, who are on disease-modifying drugs, and aged 18-65.

The study involves information about two hypothetical drugs. The information will be presented in two different ways. We want to find out which of the two ways is easiest to understand and makes you the most certain about your treatment choice.

We plan to use information we get from this study to improve the presentation of risk-benefit information about MS drugs, facilitating shared decision-making between people with MS and health professionals.

Contact: If you have any questions about this study or would like more information about this project, please speak to Noreen Barker (Specialist MS Nurse based at the Royal Free), Dr Brenner (Consultant Neurologist based at the Royal Free) or contact:

Elizabeth Donnachie, Trainee Clinical Psychologist,
Elizabeth.donnachie.2016@live.rhul.ac.uk

Appendix F

Consent form



IRAS ID: 237342

Study Number:

Participant Identification Number for this trial:

CONSENT FORM

Title of Project: Effect of risk propensity on understanding and decision-making regarding disease-modifying drugs in Multiple Sclerosis

Name of Researcher: Elizabeth ~~Donachie~~

Please initial box

1. I confirm that I have read the information sheet dated 01.03.2018 (Version 1) for the above study. I have had the opportunity to consider the information, ask questions ~~and~~ have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any ~~time~~ without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that data collected during the study, may be looked at by individuals ~~from~~ Royal Holloway University or from the NHS Trust, where it is relevant to my ~~taking~~ part in this research. I give permission for these individuals to have access ~~to~~ my records. ☐
4. I agree to take part in the above study. ☐

Name of Participant

Date

Signature

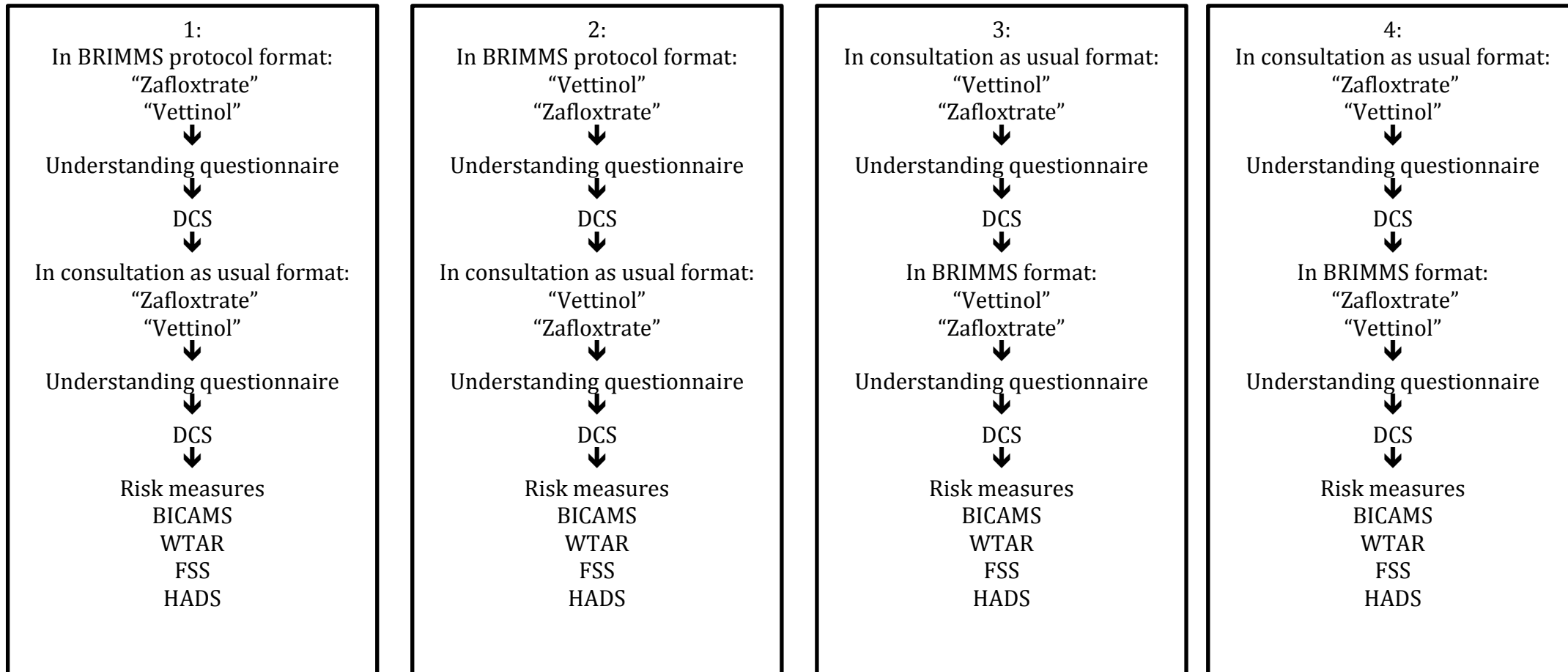
Name of Person
~~taking~~ consent

Date

Signature

Appendix G

Counterbalanced order of presentation of assessments



Trylan's Disease

The following information is about a fake medical disease, Trylan's Disease, which is a chronic medical condition (a progressive condition) and can lead to complications in the pancreas and kidneys



Without any treatment and as the disease progresses, a patient may experience the following symptoms:

- Type 2 diabetes: With progression of the disease, people are likely to develop Diabetes which would require daily management with medications
- Kidney stones: People may frequently experience kidney stones over time, which may require surgery. Regular monitoring will be required to detect kidney stones
- Kidney failure: In the very severe form of the disease, people may experience kidney failure and require

dialysis. Regular monitoring and scans during the condition will be used to detect kidney failure

Zafloxtrate

Benefits of taking Zafloxtrate

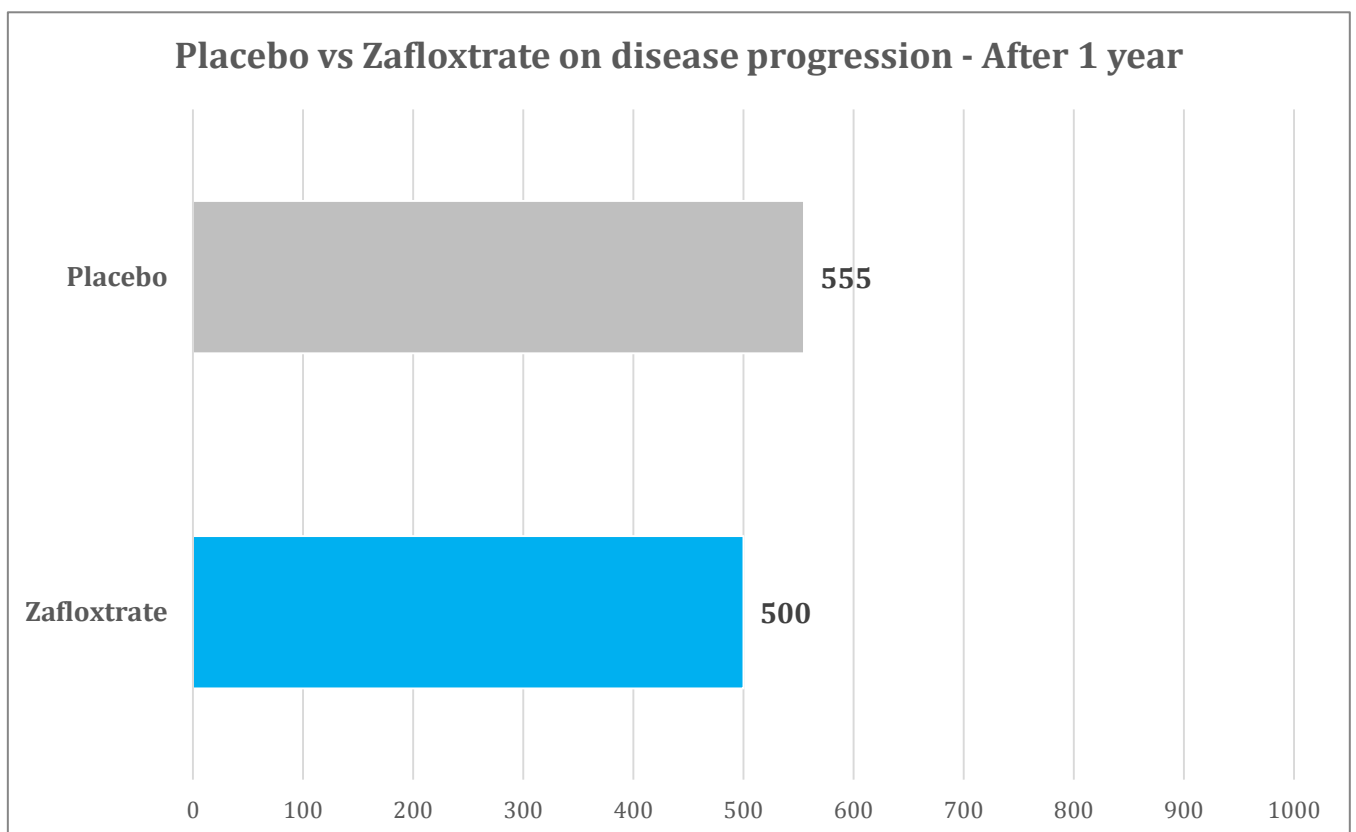
In a clinical trial, 1000 patients were given Zafloxtrate and 1000 patients were given a placebo, or a fake pill.

This was to show the benefits of taking the medication on progression of disease.

After 1 year of taking the placebo, the disease continues to progress rapidly for 555 people out of 1000

After 1 year of taking Zafloxtrate, the disease continues to progress rapidly for 500 people out of 1000

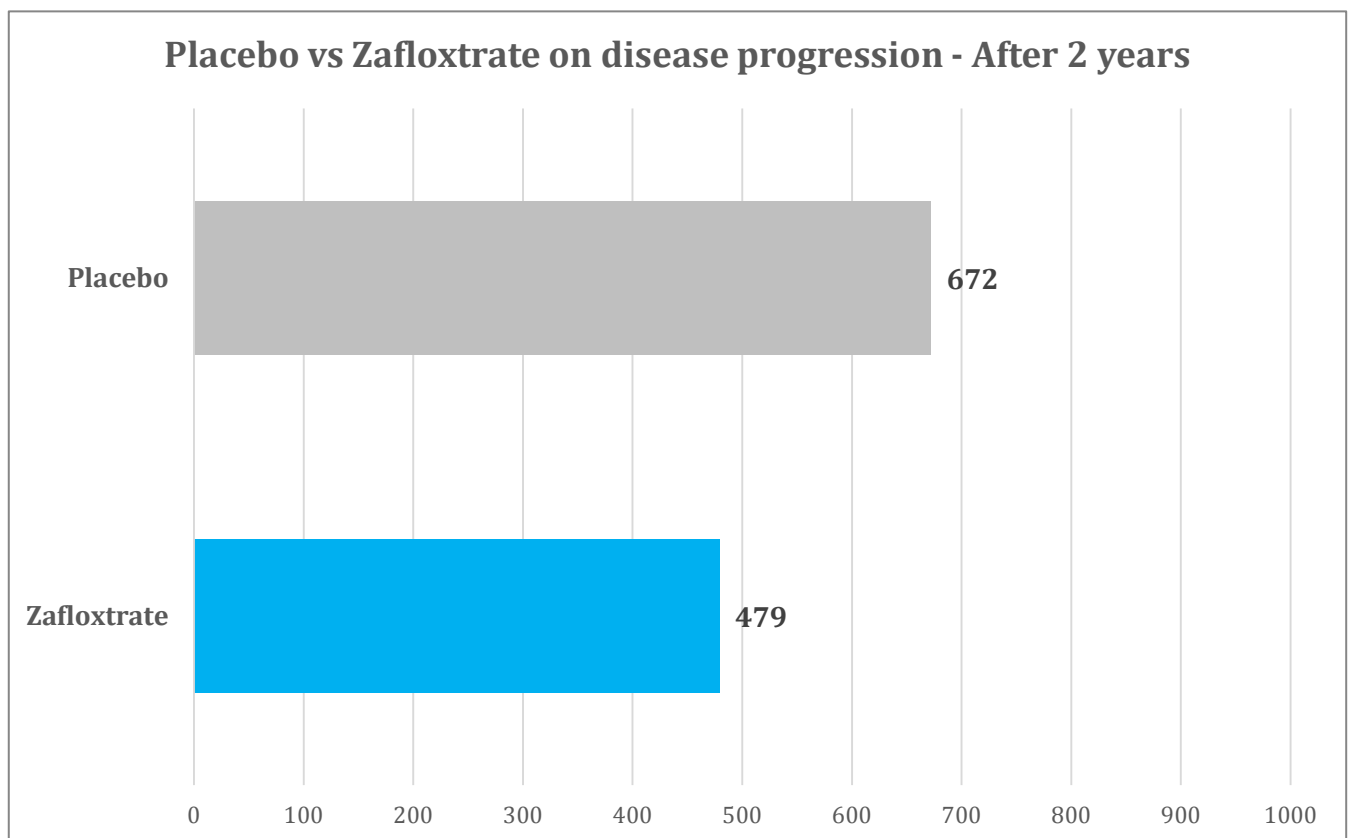
So after taking Zafloxtrate for 1 year, disease progression slowed down for 55 people



After 2 years of taking the placebo, the disease continues to progress rapidly for 672 people out of 1000

After 2 years of taking Zafloxtrate, the disease continues to progress rapidly for 479 people out of 1000

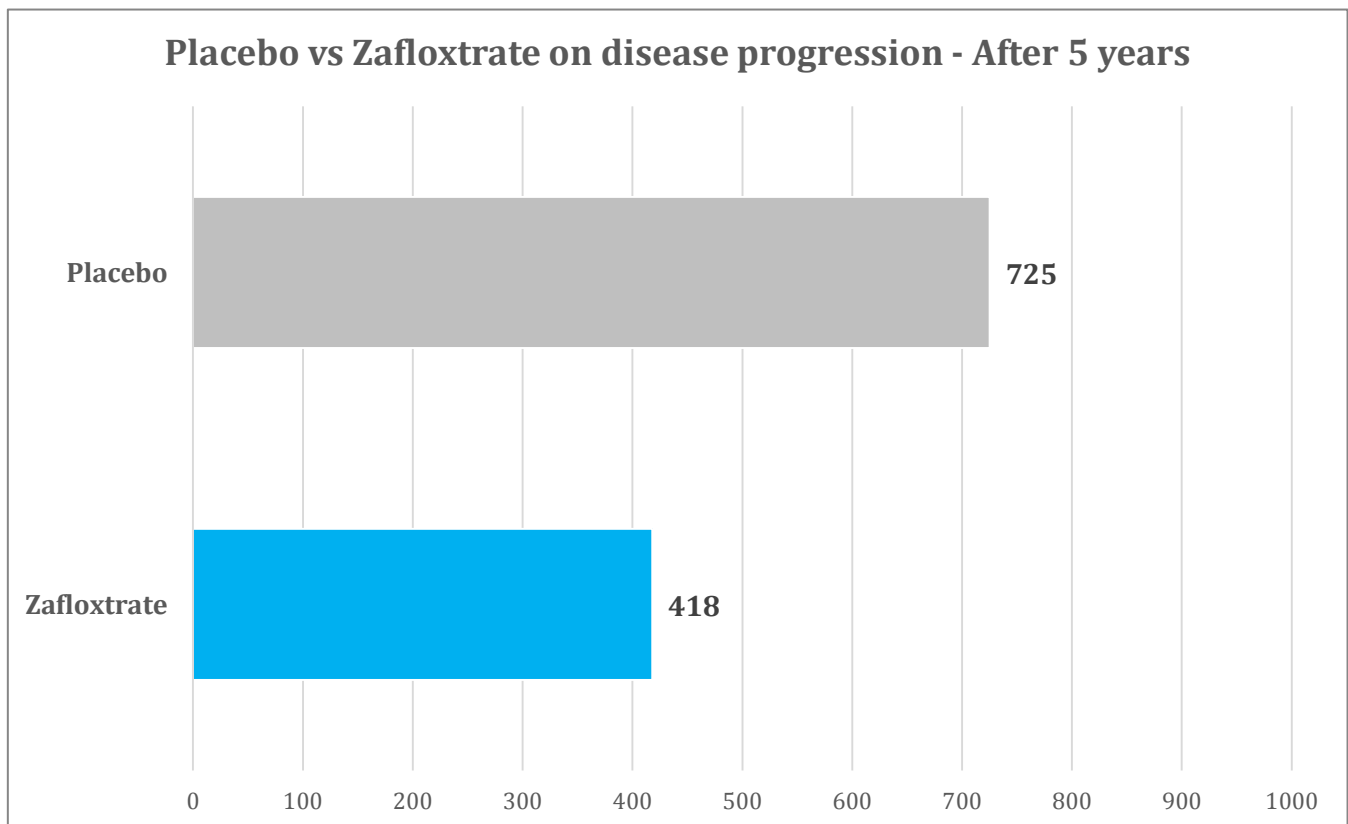
So after taking Zafloxtrate for 2 years, disease progression slowed down for 193 people



After 5 years of taking the placebo, the disease continues to progress rapidly for 725 people out of 1000

After 5 years of taking Zafloxtrate, the disease continues to progress rapidly for 418 people out of 1000

So after taking Zafloxtrate for 5 years, disease progression slowed down for 307 people



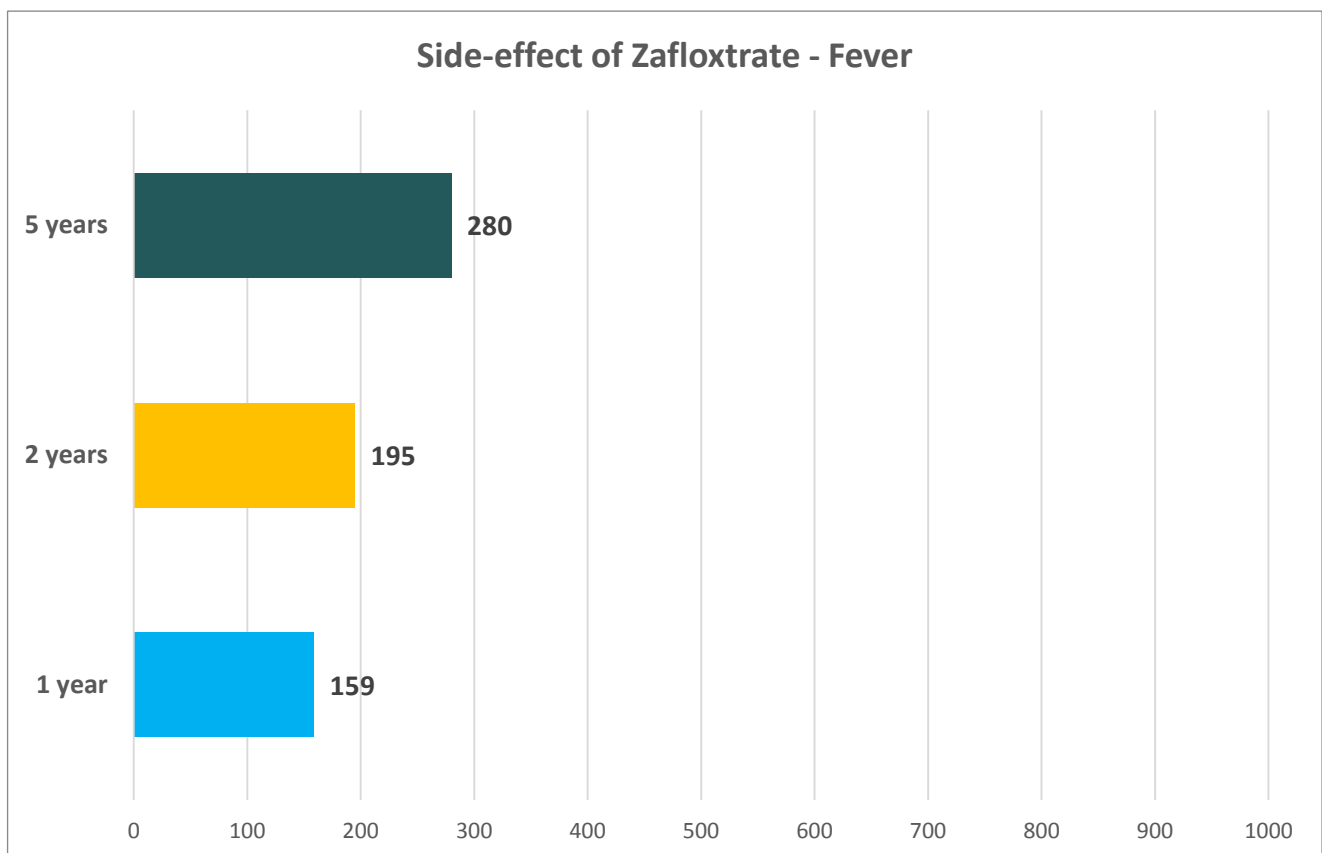
Side-effect of taking Zafloxtrate

A side-effect of taking Zafloxtrate is fever

After 1 year of taking Zafloxtrate, 159 people out of 1000 could develop fever

After 2 years of taking Zafloxtrate, 195 people out of 1000 could develop fever

After 5 years of taking Zafloxtrate, 280 people out of 1000 could develop fever



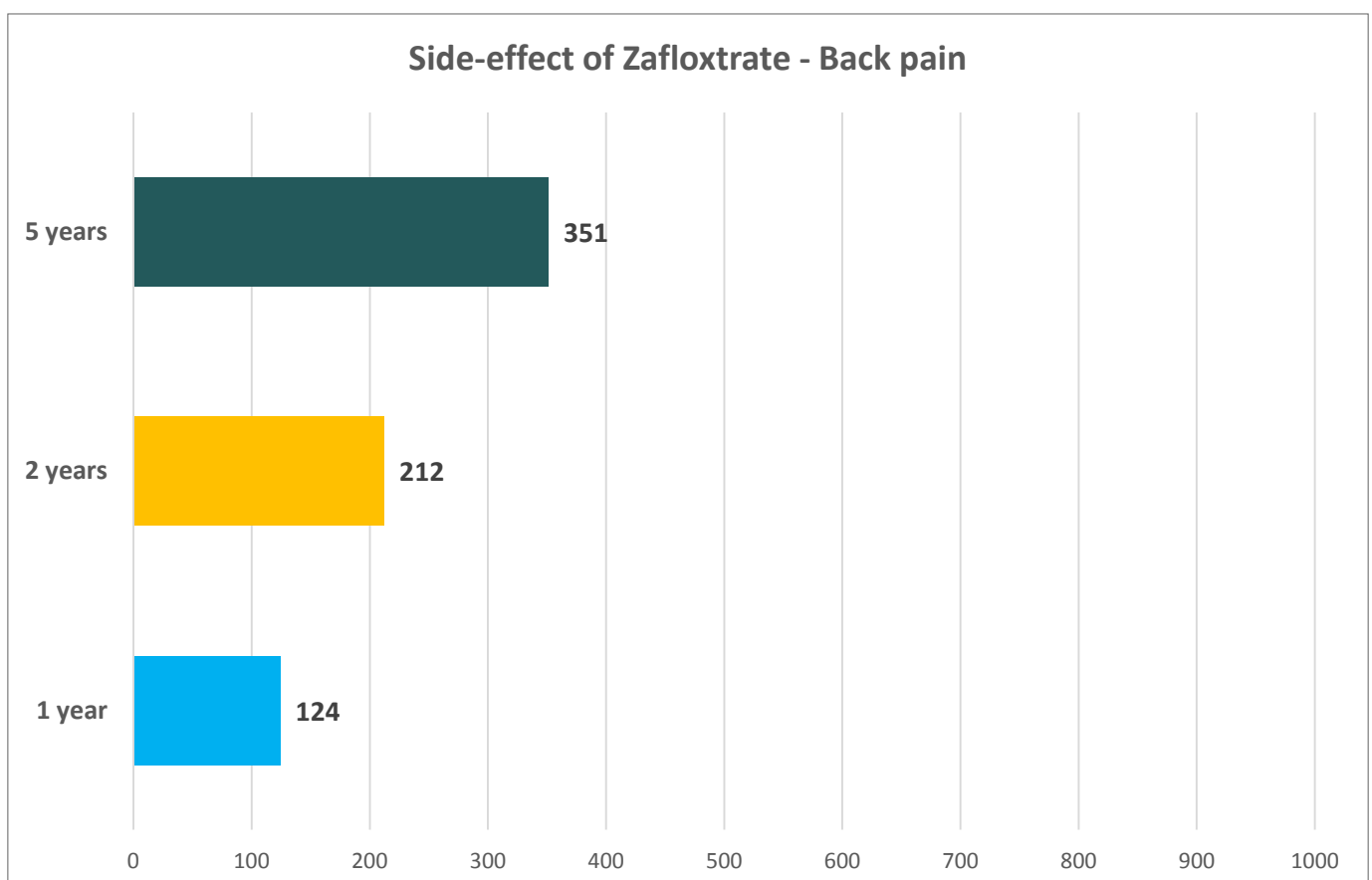
Side-effect of taking Zafloxtrate

Another side-effect of taking Zafloxtrate is back pain

After 1 year of taking Zafloxtrate, 124 people out of 1000 could develop back pain.

After 2 years of taking Zafloxtrate, 212 people out of 1000 could develop back pain.

After 5 years of taking Zafloxtrate, 351 people out of 1000 could develop back pain



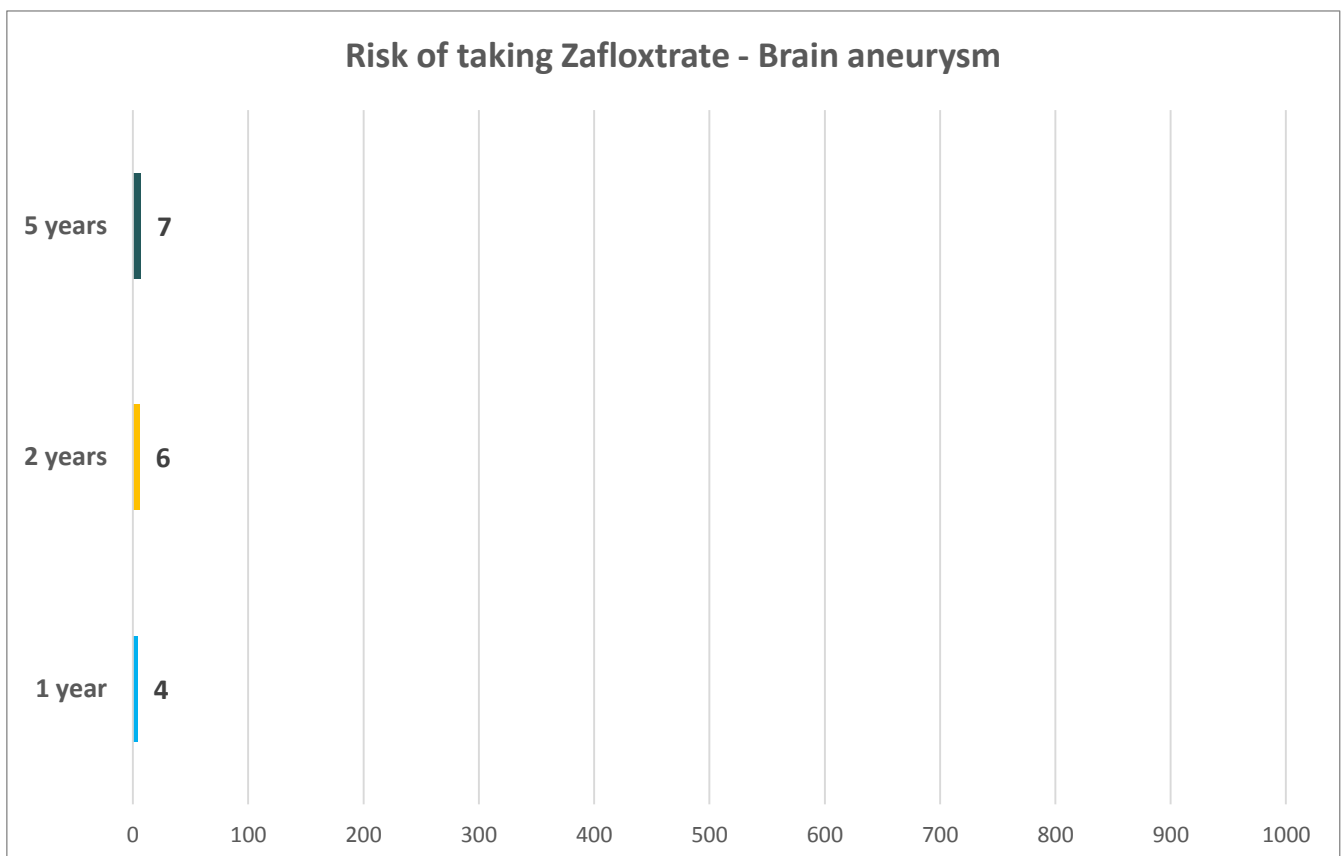
Risks of taking Zafloxtrate

A risk of taking Zafloxtrate is the risk of developing a brain aneurysm or blood clots in the brain

After 1 year of taking Zafloxtrate, 4 people out of 1000 could be at risk of brain aneurysm

After 2 years of taking Zafloxtrate, 6 people out of 1000 could be at risk of brain aneurysm

After 5 years of taking Zafloxtrate, 7 people out of 1000 could be at risk of brain aneurysm



Appendix J
Example of standard consultation

Zafloxtrate

Benefits of taking Zafloxtrate

In a clinical trial, some patients were given Zafloxtrate and some were given a placebo, a fake pill.

This showed the benefits of taking the medication on progression of disease.

After 1 year of taking Zafloxtrate, the progression of disease slowed down by 10% compared to patients taking a placebo.

After 2 years of taking Zafloxtrate, the progression of disease slowed down by 29%, compared to patients taking a placebo.

After 5 years of taking Zafloxtrate, the progression of disease slowed down by 42%, compared to patients taking a placebo.”

Side-effect of taking Zafloxtrate

A side-effect of taking Zafloxtrate is fever.

This side-effect is very common, as it effects over 1 in 100 people after 1 years, 2 years and 5 years of taking Zafloxtrate

Side-effect of taking Zafloxtrate

Another side-effect of taking Zafloxtrate is back pain.

This side-effect is very common, as it effects over 1 in 100 people after 1 years, 2 years and 5 years of taking Zafloxtrate.

Risks of taking Zafloxtrate

A risk of taking Zafloxtrate is the risk of developing a brain aneurysm or blood clots in the brain

After 1 year of taking Zafloxtrate, less than 1 in 100 people could be at risk of brain aneurysm

After 2 years of taking Zafloxtrate, less than 1 in 100 people could be at risk of brain aneurysm

After 5 years of taking Zafloxtrate, less than 1 in 100 people could be at risk of brain aneurysm

Appendix K

Understanding questions

Understanding questions

Zafloxtrate

Benefits of taking Zafloxtrate – 1 year

1. If 1000 people took Zafloxtrate for 1 year, how many people will continue to have rapid disease progression?

- ☐ 99 out of 1000
- ☐ 230 out of 1000
- ☐ 500 out of 1000
- ☐ 822 out of 1000

2. This question is about the difference between people taking Zafloxtrate and people taking the placebo.

After 1 year, how many people had slow disease progression after taking Zafloxtrate compared to placebo?

- ☐ 55 out of 1000
- ☐ 200 out of 1000
- ☐ 380 out of 1000
- ☐ 844 out of 1000

Benefits of taking Zafloxtrate – 2 years

1. If 1000 people took Zafloxtrate for 2 years, how many people will continue to have rapid disease progression?

- ☐ 82 out of 1000
- ☐ 198 out of 1000
- ☐ 479 out of 1000
- ☐ 811 out of 1000

2. This question is about the difference between people taking Zafloxtrate and people taking the placebo.

After 2 years, how many people had slow disease progression after taking Zafloxtrate compared to placebo?

- ☐ 193 out of 1000
- ☐ 350 out of 1000
- ☐ 600 out of 1000
- ☐ 845 out of 1000

Benefits of taking Zafloxtrate – 5 years

1. If 1000 people took Zafloxtrate for 5 years, how many people will continue to have rapid disease progression?

- ☐ 112 out of 1000
- ☐ 315 out of 1000
- ☐ 418 out of 1000
- ☐ 798 out of 1000

2. This question is about the difference between people taking Zafloxtrate and people taking the placebo.

After 5 years, how many people had slow disease progression after taking Zafloxtrate compared to placebo?

- ☐ 111 out of 1000
- ☐ 307 out of 1000
- ☐ 598 out of 1000
- ☐ 821 out of 1000

Side-effect of taking Zafloxtrate

1. If 1000 people took Zafloxtrate for 1 year, how many people could develop fever?

2. If 1000 people took Zafloxtrate for 2 years, how many people could develop fever?

3. If 1000 people took Zafloxtrate for 5 years, how many people could develop fever?

Side-effect of taking Zafloxtrate

1. If 1000 people took Zafloxtrate for 1 year, how many people could develop back pain?

2. If 1000 people took Zafloxtrate for 2 years, how many people could develop back pain?

3. If 1000 people took Zafloxtrate for 5 years, how many people could develop back pain?

Risk of taking Zafloxtrate

1. If 1000 people took Zafloxtrate for 1 year, how many people could be at risk of brain aneurysm?

2. If 1000 people took Zafloxtrate for 2 years, how many people could be at risk of brain aneurysm?

3. If 1000 people took Zafloxtrate for 5 years, how many people could be at risk of brain aneurysm?

Appendix L

Decisional Conflict Scale

Traditional Decisional Conflict Scale (DCS) – Statement Format: 16 item 5 response categories (O'Connor, 1995)

My difficulty in making this choice

A. Which treatment option do you prefer? Please tick one:

Option 1-Zafloxtrate

Option 2-Vettinol

Option 3-No treatment

Option 4-Unsure

B. Considering the option you prefer, please answer the following questions:

	Strongly Agree	Agree	Neither Agree Nor Disagree	Disagree	Strongly Disagree
1. I know which options are available to me.					
2. I know the benefits of each option.					
3. I know the risks and side effects of each option.					
4. I am clear about which benefits matter most to me.					
5. I am clear about which risks and side effects matter most to me.					
6. I am clear about which is more important to me (the benefits or the risks and side effects).					
7. I have enough support from others to make a choice.					
8. I am choosing without					

pressure from others.					
9. I have enough advice to make a choice.					
10. I am clear about the best choice for me.					
11. I feel sure about what to choose.					
12. This decision is easy for me to make.					
13. I feel I have made an informed choice.					
14. My decision shows what is important to me.					
15. I expect to stick with my decision.					
16. I am satisfied with my decision.					

Appendix M

Risk measure

Risk Attitudes and Risk Perceptions Questionnaire for Individuals with Multiple Sclerosis

1. In general, people often face risks when making financial, career or other life decisions. Overall, how would you place yourself on the following scale from 1-7?

Extremely Comfortable Taking Risks			Neither Comfortable Nor Uncomfortable Taking Risks			Extremely Uncomfortable Taking Risks	
1	2	3	4	5	6	7	

2. Please indicate the extent to which you agree or disagree with the following statement by putting a circle around the option you prefer. Please do not think too long before answering; usually your first inclination is also the best one.

	Totally Disagree			Neither Agree Nor Disagree			Totally Agree		
Safety first.	1	2	3	4	5	6	7	8	9
I do not take risks with my health.	1	2	3	4	5	6	7	8	9
I prefer to avoid risks.	1	2	3	4	5	6	7	8	9
I take risks regularly.	1	2	3	4	5	6	7	8	9
I really dislike not knowing what is going to happen.	1	2	3	4	5	6	7	8	9
I usually view risks as a challenge	1	2	3	4	5	6	7	8	9

	Risk Avoider						Risk Seeker		
I view myself as a...	1	2	3	4	5	6	7	8	9

3. Please indicate whether you are currently taking any disease modifying medication for your MS?

- | | | |
|---|--|--|
| <input type="checkbox"/> ₁ Aubagio | <input type="checkbox"/> ₅ Extavia | <input type="checkbox"/> ₉ Rebif |
| <input type="checkbox"/> ₂ Avonex | <input type="checkbox"/> ₆ Gilenya | <input type="checkbox"/> ₁₀ Tecfidera |
| <input type="checkbox"/> ₃ Betaseron | <input type="checkbox"/> ₇ Novantrone | <input type="checkbox"/> ₁₁ Tysabri |
| <input type="checkbox"/> ₄ Copaxone | <input type="checkbox"/> ₈ Plegridy | <input type="checkbox"/> ₁₂ Other : _____ |

4. Please estimate the risk of your MS worsening over the short- (2 years), medium- (5 years) and long-term (10 years).

	Extremely Unlikely	Unlikely	Neither Likely Nor Unlikely	Likely	Extremely Likely
2 years	1	2	3	4	5
5 years	1	2	3	4	5
10 years	1	2	3	4	5

5. Please estimate the risk of **minor side effects** associated with each of the following disease modifying therapies:

	Extremely Unlikely	Unlikely	Neither Likely Nor Unlikely	Likely	Extremely Likely	Don't Know
Avonex	1	2	3	4	5	<input type="checkbox"/>
Betaseron	1	2	3	4	5	<input type="checkbox"/>
Copaxone	1	2	3	4	5	<input type="checkbox"/>
Gilenya	1	2	3	4	5	<input type="checkbox"/>
Rebif	1	2	3	4	5	<input type="checkbox"/>
Tecfidera	1	2	3	4	5	<input type="checkbox"/>
Tysabri	1	2	3	4	5	<input type="checkbox"/>

6. Please estimate the risk of **serious side effects** associated with each of the following disease modifying therapies:

	Extremely Unlikely	Unlikely	Neither Likely Nor Unlikely	Likely	Extremely Likely	Don't Know
Avonex	1	2	3	4	5	<input type="checkbox"/>
Betaseron	1	2	3	4	5	<input type="checkbox"/>
Copaxone	1	2	3	4	5	<input type="checkbox"/>
Gilenya	1	2	3	4	5	<input type="checkbox"/>
Rebif	1	2	3	4	5	<input type="checkbox"/>
Tecfidera	1	2	3	4	5	<input type="checkbox"/>
Tysabri	1	2	3	4	5	<input type="checkbox"/>

7. Imagine that there is a new MS drug. If you take the drug, you will have no new relapses and your MS will not worsen. The drug, however, may cause death. How likely are you to take the drug if the risk of death is:

Risk of Death	Extremely Unlikely	Unlikely	Neither Likely Nor Unlikely	Likely	Extremely Likely
1 in 2	1	2	3	4	5
1 in 10	1	2	3	4	5
1 in 100	1	2	3	4	5
1 in 1,000	1	2	3	4	5
1 in 10,000	1	2	3	4	5
1 in 100,000	1	2	3	4	5

Appendix N
Symbol Digit Modalities Test (SDMT)

KEY

(÷	┐	┌	┐	>	+)	÷
1	2	3	4	5	6	7	8	9

(┐	÷	(┐	>	÷	┌	(>	÷	(>	(÷

┌	>	(÷	┐	>	┐	┌	(÷	>	÷	┌	┐)

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÷	┌	┐	(>	┌	(┐	>	+	÷)	┐	>	┌

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Appendix O

California Verbal Learning Task II (CVLT-II)

Read List A at an even pace, taking slightly longer than one second per word, so the entire list takes 18 to 20 seconds. Then say, Go ahead.

List A

- truck
- spinach
- giraffe
- bookcase
- onion
- motorcycle
- cabinet
- zebra
- coach
- lamp
- celery
- cow
- desk
- boat
- squirrel
- cabbage

Trial 1

Resp Type

1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	

Total Correct C ☐

Total Repetitions R ☐

Total Intrusions I ☐

Trial 2

Resp Type

1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	

Total Correct C ☐

Total Repetitions R ☐

Total Intrusions I ☐

Trial 3

Resp Type

1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	

Total Correct C ☐

Total Repetitions R ☐

Total Intrusions I ☐

Trial 4

Resp Type

1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	

Total Correct C ☐

Total Repetitions R ☐

Total Intrusions I ☐

Trial 5

Resp Type

1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	

Total Correct C ☐

Total Repetitions R ☐

Total Intrusions I ☐

List A Immediate Free Recall Trial 1

I'm going to read a list of words to you. Listen carefully, because when I'm through, I want you to tell me as many of the words as you can. You can say them in any order, just say as many of them as you can. Are you ready?

Read List A at an even pace, taking slightly longer than one second per word, so the entire list takes 18 to 20 seconds. Then say, Go ahead.

Trial 2

I'm going to read the same list again. Like before, tell me as many of the words as you can, in any order. Be sure to also say words from the list that you told me the first time.

Record all responses verbatim, in the order recalled. Prompt only once (e.g., Anything else?) at the end of each and record recall trial (i.e., after 15 seconds with no response or when the examinee says he/she cannot remember more words).

Trials 3 and 4

I'm going to read the same list again. Like before, tell me as many of the words as you can, in any order, including words from the list you've said before.

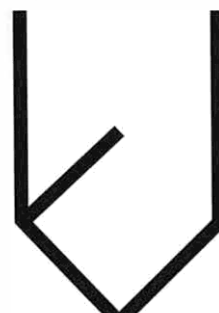
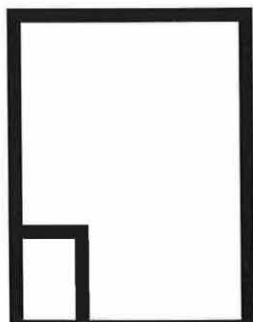
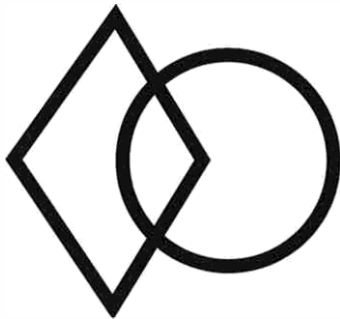
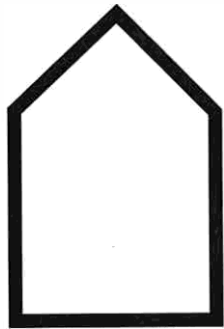
Trial 5

I'm going to read the same list one more time. Like before, tell me as many of the words as you can, in any order, including words from the list you've said before.

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Appendix P

Brief Visuospatial Memory Test- Revised (BVMT-R)



Appendix Q

Weschler Test of Adult Reading (WTAR)

Appendix R

Hospital Anxiety and Depression Scale (HADS)

Appendix S

Fatigue Severity Scale (FSS)

Fatigue Severity Scale (FSS)

The Fatigue Severity Scale (FSS) is a method of evaluating the impact of fatigue on you. The FSS is a short questionnaire that requires you to rate your level of fatigue.

The FSS questionnaire contains nine statements that rate the severity of your fatigue symptoms. Read each statement and circle a number from 1 to 7, based on how accurately it reflects your condition during the past week and the extent to which you agree or disagree that the statement applies to you.

- A low value (e.g., 1) indicates strong disagreement with the statement, whereas a high value (e.g., 7) indicates strong agreement.
- It is important that you circle a number (1 to 7) for every question.

FSS Questionnaire

During the past week, I have found that:	Disagree	←	→	Agree			
1. My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
8. Fatigue is among my three most disabling symptoms.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7
Total Score:							

Appendix T

Correlations between fatigue, anxiety, depression and cognition

A Pearson product-moment correlation was conducted to examine the relationship between fatigue, anxiety, depression and cognition. There was a significant positive correlation between depression and anxiety, higher levels of depression were associated with higher levels of anxiety ($r(24)=.79, p<.01$). There was a significant positive correlation between depression and fatigue, higher levels of depression were associated with higher levels of fatigue ($r(24)=.66, p<.01$). There was a significant positive correlation between anxiety and fatigue, higher levels of anxiety were associated with higher levels of fatigue ($r(24)=.56, p<.01$). There was a significant negative correlation between depression and cognition ($r(24)= -.46, p<.05$), anxiety and cognition ($r(24)=-.55, p<.05$) and fatigue and cognition ($r(24)=-.49, p<.01$). That is, higher levels of depression, anxiety and fatigue were associated with lower cognition.

Appendix U

Descriptive statistics for demographic variables

	Gender	Age		Ethnicity	Level of Education	Employment	Premorbid IQ		
<i>N</i>	M:F	\bar{x} (<i>SD</i>)	Range	WB:BB:WI:AB *	S:C:B:P**	F:P:MR:R***	\bar{x} (<i>SD</i>)	Range	Max. total score
26	7:19	43.38 (10.32)	24-60	19:4:2:1	4:6:8:8	14:3:4:5	101.65 (14.09)	67-120	120

*WB: White British; BB: Black British; WI: White Irish; AB: Asian British

**S: Secondary School; C :College; B :Bachelors degree; P: Post-graduate

***F: Full-time; P: Part-time; MR: Medically Retired; R: Retired

Appendix V

Descriptive statistics for clinical variables

Years since diagnosis		EDSS		Current DMD		FSS		HADS-D			HADS-A		
\bar{x} <i>(SD)</i>	Range	\bar{x} <i>(SD)</i>	Range	I:G:T:F:A:D:N*	\bar{x} <i>(SD)</i>	Range	Max. total score	\bar{x} <i>(SD)</i>	Range	Max. total score	\bar{x} <i>(SD)</i>	Range	Max. total score
9.35 (6.50)	1-26	2.81 (2.45)	2.5-10	4:2:1:7:3:5:4	37.85 (18.81)	9-63	63	4.58 (3.87)	0-12	21	7.96 (4.40)	2-17	21

*I:Interferon beats; G:Glatiramer Acetate; T:Teriflunomide; F:Fingolimod; A:Alemtuzumab; D:Dimethyl Fumarate; N:Natalizumab

Appendix W

Descriptive statistics for cognitive tests

SDMT			CVLT-II			BVMT-R		
\bar{x}	Range	Max. total	\bar{x}	Range	Max. total	\bar{x}	Range	Max.
(<i>SD</i>)		score	(<i>SD</i>)		score	(<i>SD</i>)		total score
50.92	18-74	110	48.35	28-75	80	21.27	4-36	36
(13.91)			(12.85)			(9.05)		